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The New England Journal of Medicine

FORMERLY THE BOSTON MEDICAL AND SURGICAL JOURNAL — *Established 1828*

VOLUME 248 JUNE 25, 1953 NUMBER 26

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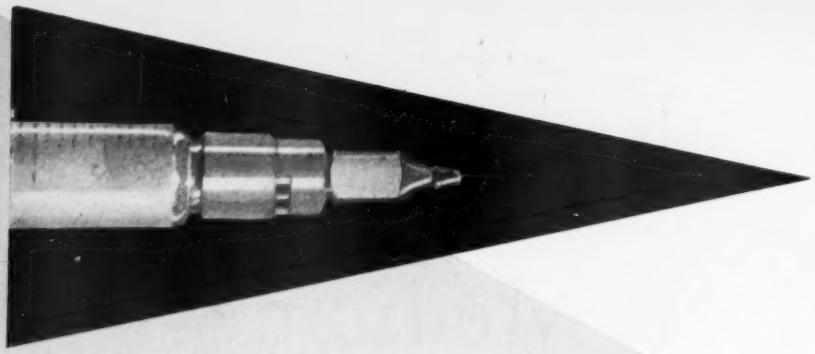

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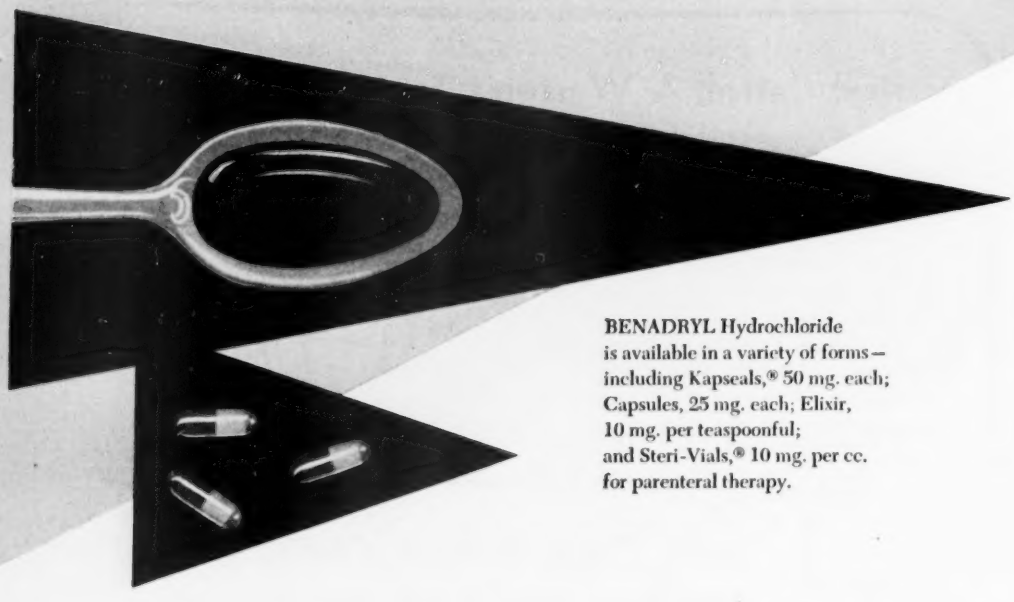

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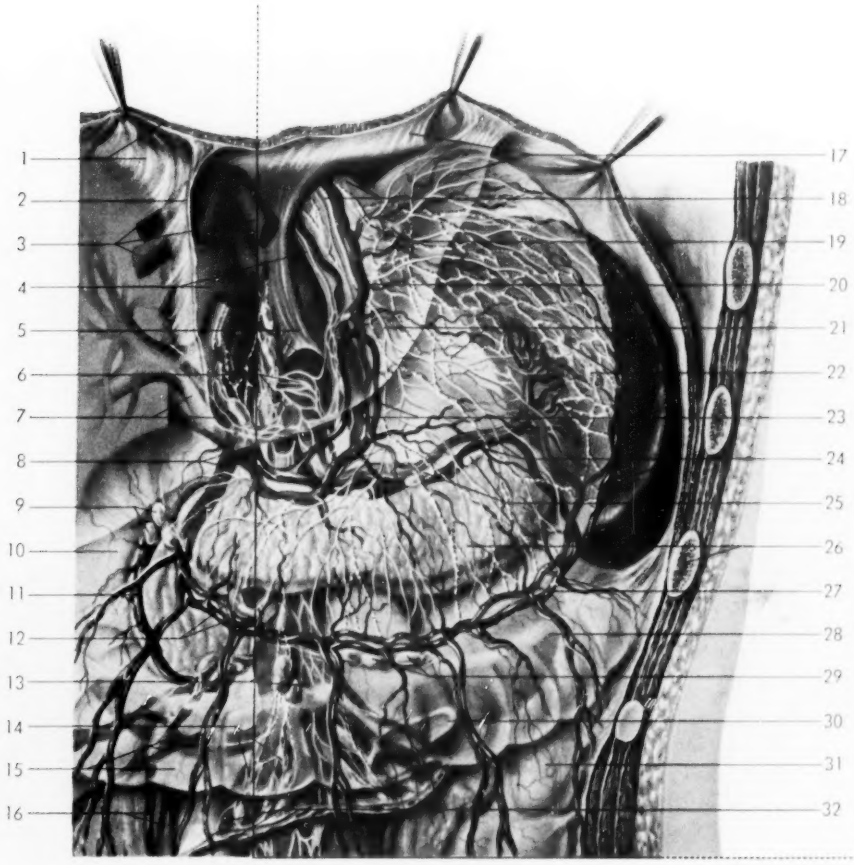

1 Diaphragm and coronary ligament
2 Falciform ligament
3 Hepatic veins
4 Inferior vena cava and right vagus nerve
5 Crus of diaphragm and abdominal aorta
6 Celiac artery and celiac plexus
7 Hepatic artery and portal vein
8 Gastroduodenal artery and vein
9 Subpyloric lymph nodes
10 Duodenum
11 Superior pancreaticoduodenal artery and vein
12 Right gastroepiploic artery and vein
13 Superior mesenteric artery and vein
14 Superior mesenteric lymph nodes
15 Transverse colon and right colic artery and vein
16 Spermatic artery and vein
17 Left triangular ligament and left lobe of liver
18 Esophagus and left vagus nerve
19 Paracardial lymph nodes
20 Esophageal branch of left gastric artery and vein
21 Gastric rami of vagus nerve
22 Splenic lymph nodes
23 Left gastric artery and coronary vein
24 Spleen and splenic artery and vein
25 Superior pancreatic lymph nodes
26 Pancreas and tenth rib
27 Left gastroepiploic artery and vein
28 Left kidney
29 Inferior gastric lymph nodes
30 Jejunum
31 Descending colon
32 Ileocolic artery and vein

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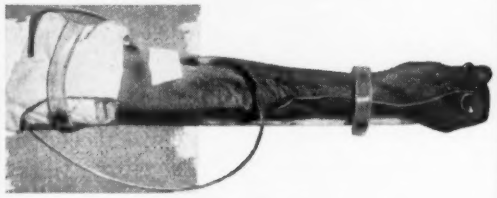

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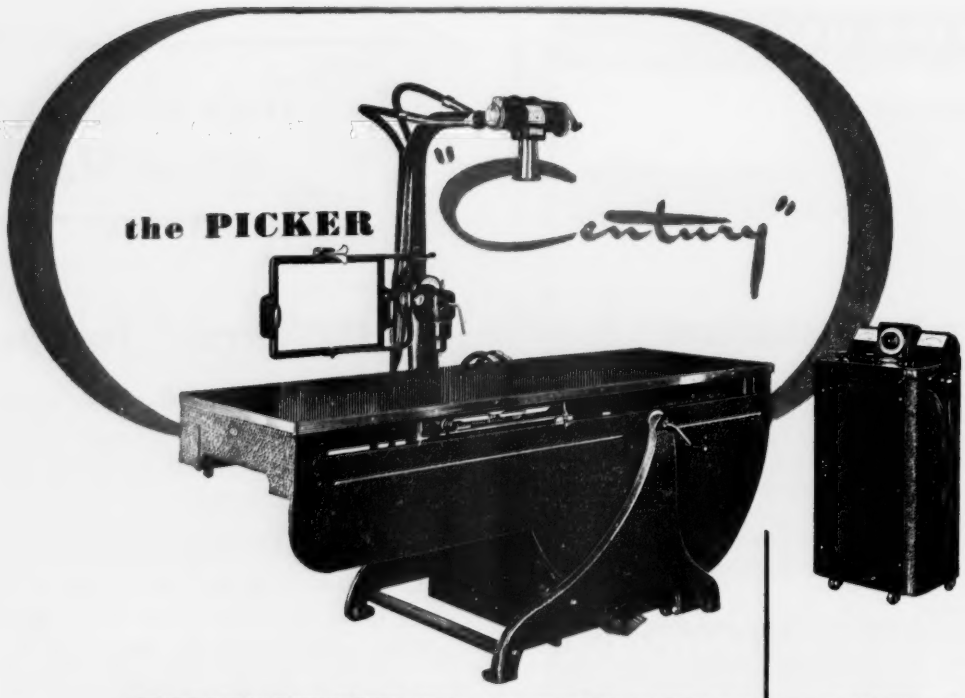

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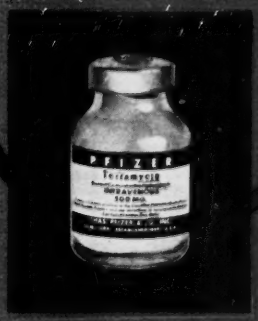

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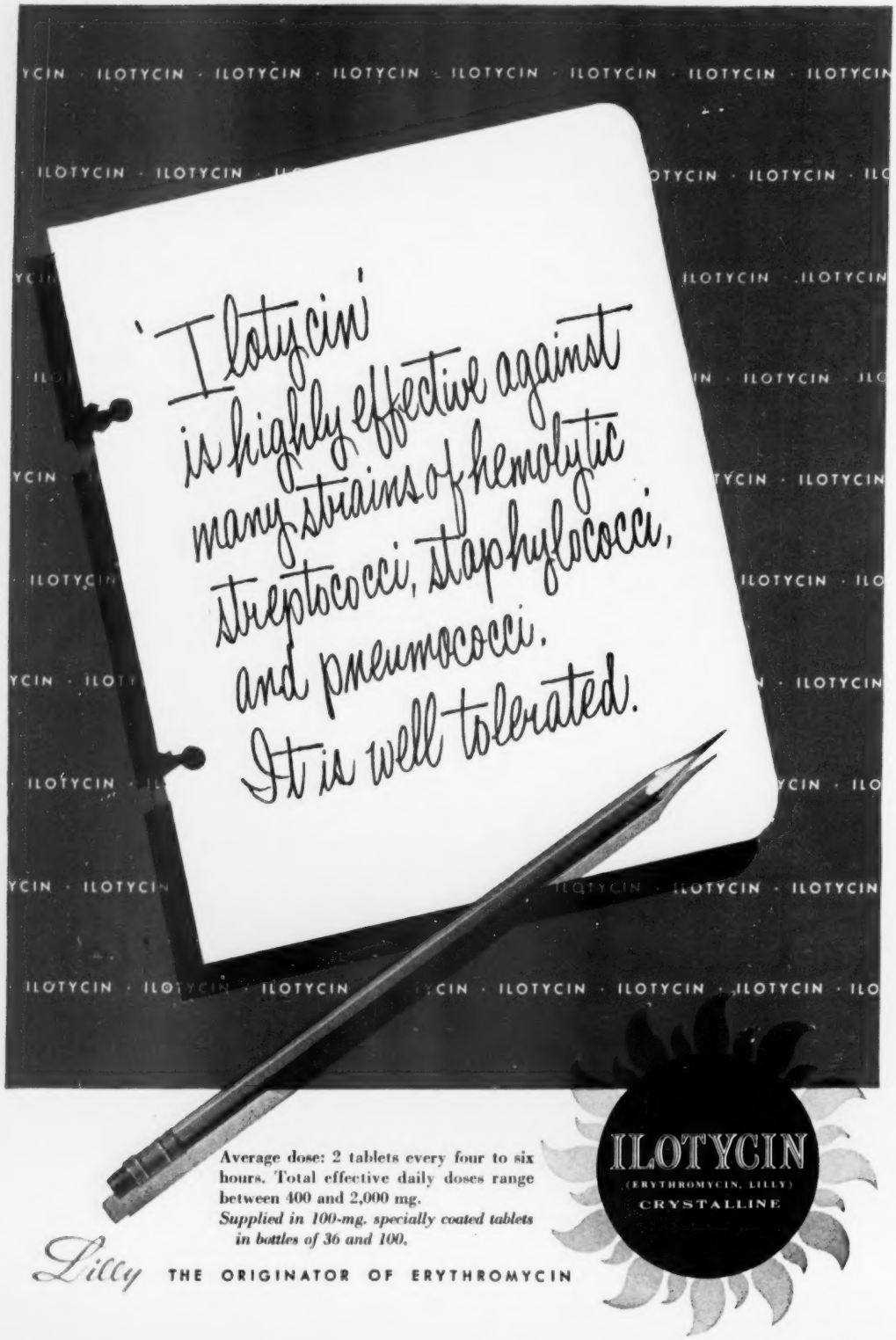
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THE CLINICAL SIGNIFICANCE OF THE EMERGENCE OF DRUG-RESISTANT ORGANISMS DURING THE THERAPY OF CHRONIC PULMONARY TUBERCULOSIS WITH HYDRAZIDES OF ISONICOTINIC ACID*

E. O. Coates, Jr., M.D.,† G. M. Meade, M.D.,‡ William Steenken, Jr., M.D.,§
E. Wolinsky, M.D.,¶ and G. L. Brinkman, M.D.||

TRUDEAU, NEW YORK

SOON after the discovery of the potent antituberculosis effect of the isoniazid drugs in laboratory animals in 1951, a number of reports appeared describing their value in patients with pulmonary tuberculosis.[1,2] Emergence of drug-resistant tubercle bacilli, or indication of such a phenomenon, was not reported in those studies although observations soon became available demonstrating that increased bacterial resistance to the drugs may appear rapidly during therapy with either isoniazid or iproniazid alone.[3-9] The relative frequency and consistency of this phenomenon during isoniazid therapy have recently been confirmed by large and carefully controlled studies.[10-13] However, uncertainty still exists regarding the clinical significance of the development of isoniazid-resistant tubercle bacilli, and definitive information is needed concerning the relation of slight or higher degrees of bacterial resistance to the patients' clinical course. Investigation of this particular question is the subject of the present report.

Materials and Methods

The 43 patients with whom this report deals are derived from an original group of 55 started on therapy with isonicotinic acid hydrazides (INH)** in a co-operative study. Participants in the study included Trudeau Sanatorium, Ray Brook State Tuberculosis Hospital, Sanatorium Gabriels, Variety Clubs-Will Rogers Hospital and Stony Wold Sanatorium, as well as 5 physicians in private practice.†† Most of the work on bacterial resistance was carried out by the Trudeau Laboratory of the Trudeau Sanatorium and Foundation; important contributions were also made by the laboratories of Ray Brook State Tuberculosis Hospital, Variety Clubs-Will Rogers Hospital and Stony Wold Sanatorium.‡‡

Twelve patients were lost from the original group. Seven died in the fourth to tenth weeks of therapy. Of these, 1 had signs of meningitis in the fourth week and quickly succumbed; permission for autopsy was not obtained. One died of right-sided heart failure in the sixth week of treatment. One patient had a fatal hemorrhage following a long and difficult pulmonary resection. Another patient in good general clinical condition with moderately advanced pulmonary tuberculosis died suddenly after ten days of iproniazid therapy; no ascertainable cause of death could be found at autopsy. The remaining 3 died of complications associated with advanced tuberculosis.

Four patients were not included because of the addition of other chemotherapeutic agents before the completion of sixteen weeks of INH therapy, and 1 was omitted because he left the sanatorium against advice.

The remaining 43 completed at least 16 weeks of uninterrupted therapy, 27 on isoniazid§§ and 16 on its isopropyl derivative, iproniazid.¶¶ The dosage used was 4 mg. per kilogram of body weight, averaging 200 to 300 mg. a day by mouth. Close clinical and laboratory contact was maintained with each patient throughout the period of treatment. Clinical examinations were made at intervals

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**Kindly supplied by Hoffmann-La Roche Incorporated, Nutley, New Jersey, as Rimifon (isoniazid) and Marsilid (iproniazid) respectively.

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§§Isoniazid = isonicotinic acid hydrazide.

¶¶Iproniazid = 1-isonicotinyl-2-isopropyl hydrazine.

of a week, or more frequently. Complete blood counts, sedimentation rates and urinalyses were done first at intervals of a week and later every two weeks. Screening blood urea nitrogen and thymol turbidity tests were performed before treatment and as indicated thereafter.

Stereoscopic posteroanterior chest films and body-section films of cavity areas were made before treatment in each case, with repeat examinations at two-week and six-week intervals respectively.

Seventy-two-hour sputum samples were obtained from each patient before treatment and at weekly intervals thereafter. After weighing, the sputum specimens were digested with sodium hydroxide and concentrated according to the technic routinely used in the Trudeau Laboratory. From this material smears and cultures were made. The smears were stained by the Ziehl-Neelsen procedure, and duplicate slides examined for ten minutes each. The relative number of acid-fast bacilli was indicated as follows:

Gaffky O-None
I-Total of 1 to 4 bacilli
II-Average of 1 bacillus in several fields
III-Average of 1 bacillus per field and so forth
X-Over 100 bacilli in each field

Although it is realized that the Gaffky count is not a completely quantitative method for reporting the number of bacilli in a specimen, it is believed that serial determinations on seventy-two-hour sputum samples, all carried out with a uniform technic by the same experienced technicians, indicate definite trends in the bacillary content.

We made cultures by planting the material thus obtained from the sputum on American Trudeau Society solid egg-yolk, potato, glycerin medium and made direct drug-sensitivity tests at the same time, as previously described,[3] by planting equal amounts on tubes of the same medium containing graded concentrations of the drugs. For isoniazid, concentrations of 0.2, 1.0, 5.0 and 10 microgm. per cubic centimeter and for iproniazid, concentrations of 2.5, 10, 30 and 100 microgm. per cubic centimeter were used. The amount and rapidity of appearance of growth in the tubes of drug-containing medium was then compared with that in the control tubes of plain medium. In the event that less than 50 colonies appeared in each of the two control tubes, we subcultured a representative sample of the colonies in liquid Tween-albumin medium, and tested the resultant pure culture by planting a double loopful on tubes of solid medium containing the same drug concentrations as those used for the direct test.

Criteria for selection of patients for this study were failure to improve on conventional forms of therapy, including streptomycin and PAS, and cavitary cases with positive sputums that might be anticipated to provide a continuing source of bacilli. The latter criterion was chosen to afford adequate material for observations on the development of bacterial resistance to these compounds—a basic aim of the investigation.

Thus, the group comprised a selected population of patients with predominantly chronic, cavitary disease, the majority of whom had had prolonged treatment with streptomycin and PAS, and often collapse therapy as well. Table 1 shows that far-advanced disease was present in about 80 per cent of the entire group of 43 patients at the start of treatment. A similar percentage of patients over the age of thirty-five indicates that the patients were considerably older than those usually encountered in a sanatorium population. Comparison of the background factors in the isoniazid and iproniazid groups reveals them to be quite similar in age, extent of disease and size of cavities before treatment. General clinical condition, however, was not as good in the isoniazid group, 52 per cent

TABLE 1. *Background Data of INH Treatment Groups before Start of Therapy.*

GROUP	MALE PATIENTS	FEMALE PATIENTS	PATIENTS 20-34 YR. OF AGE	PATIENTS 35 YR. OF AGE OR OVER	PATIENTS WITH FAR-ADVANCED DISEASE	PATIENTS WITH MODERATELY ADVANCED DISEASE
Treatment with isoniazid	2 (7%)	25 (93%)	6 (22%)	21 (78%)	22 (81%)	5 (19%)
Treatment with iproniazid	9 (56%)	7 (44%)	2 (12%)	14 (88%)	13 (81%)	3 (19%)
Totals	11 (26%)	32 (74%)	8 (19%)	35 (81%)	35 (81%)	8 (19%)

TABLE 2. *Benefit in Roentgenographic Appearance and "Relapse" under Treatment in 43 Patients during Sixteen Weeks of INH Therapy.*

COURSE DURING TREATMENT	NO. OF CASES	PERCENTAGE
Improvement in infiltration:		
Slight	15	35
Moderate or marked	3	7
All degrees	18	42
Improvement in cavity:		
Slight decrease	12	28
Moderate or marked decrease	9	21
Disappearance	4	9
"Relapse" during treatment:		
Increase in infiltration	5	12
Enlargement of cavity	15	35
Reappearance of cavity	3	7

of these patients being considered in poor condition before treatment, as opposed to 38 per cent of those treated with iproniazid.

Clinical Results of Therapy

Since our main interest at present is the problem of the development of bacterial resistance and its clinical implications, results of therapy are considered only briefly.

First, as noted by others,[1,2,10] general clinical improvement was the most striking and consistent change observed during treatment. Increased appetite, steady weight gain, decrease in cough and sputum, and improvement in general well-being were prominent features, particularly in the patients treated with iproniazid, 65 per cent of whom gained more than 11 pounds, as compared with only 15 per cent of those treated with isoniazid. This appears particularly significant when it is realized that many of these patients had been losing weight steadily before the start of treatment.

Radiographic changes were, on the whole, unimpressive. Diminution in cavity size was the commonest form of improvement, but was often only transient. The cavity disappeared in only 4 patients; of these, the cavity remained closed in only 1 during the period of treatment. Table 2 summarizes these results.

Twenty-nine (67 per cent) of the 43 patients exhibited a decrease of 4 or more Gaffky units in the bacillary count of concentrated sputum smears, sustained for two weeks or more, but only 8 specimens (18 per cent) converted to negative on culture. Furthermore, the "bacteriologic relapse rate" was high; 3 of the 8 that had converted to negative on culture became positive before sixteen weeks had elapsed, and sputum bacillary counts reverted to previous levels in 14 (Table 3).

Results of therapy with isoniazid and iproniazid in this group were closely similar, except for general clinical improvement, in which iproniazid was definitely superior.

Emergence of Drug-Resistant Organisms

A graphic representation of the bacteriologic and drug-sensitivity status of all patients during each week of therapy is presented in Figure 1. Percentages are based on the entire group of 43 patients. The "resistant" area includes all patients whose organisms demonstrated increased drug resistance, according to one of the following three classifications: "slight resistance," which comprises those whose cultures showed growth comparable to or only slightly less than the control in the lowest concentrations used—namely, 0.2 microgm. of isoniazid or 2.5 microgm. of iproniazid per cubic centimeter; "intermediate resistance," denoting cultures that showed growth comparable to or only slightly less than the control in tubes containing 0.2 *and* 1.0 microgm. of isoniazid or 2.5 *and* 10 microgm. of iproniazid per cubic centimeter, *without* significant growth in higher concentrations; and "high resistance," which consists of all cultures showing

Table 1 (*Concluded*).

Patients with No Cavity	Patients with Cavities 0-2 Cm. in Size	Patients with Cavities 2-6 Cm. in Size	Patients with Cavities More Than 6 Cm. in Size	Patients with Indeterminate Cavities	Patients in Good Clinical Condition	Patients in Fair Clinical Condition	Patients in Poor Clinical Condition
0	4 (15%)	12 (45%)	10 (37%)	1 (4%)	4 (15%)	9 (33%)	14 (52%)
1 (6%)	3 (19%)	8 (50%)	4 (25%)	0	2 (12%)	8 (50%)	6 (38%)
1 (2%)	7 (16%)	20 (47%)	14 (33%)	1 (2%)	6 (14%)	17 (40%)	20 (47%)

Table 3. *Bacteriologic Response and "Relapse" under Treatment in 43 Patients during Sixteen Weeks of INH Therapy.*

Bacteriologic Finding	No. of Cases	Percentage
Sputum Gaffky count:		
Decrease of 4 or more units sustained for at least 2 wk.	29	67
Reversion to previous status	14	33*
Sputum conversion by culture	8	19
Reversion to positive culture	3	7

*48% of 29 cases.

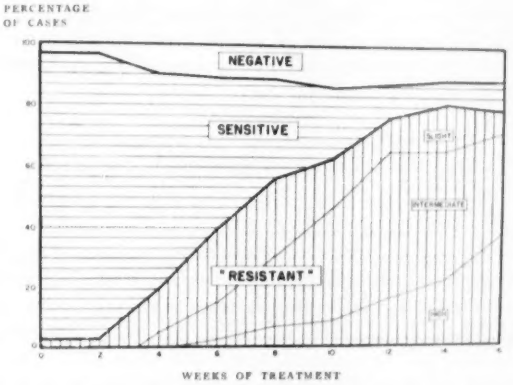

Figure 1. *Sputum Bacteriology and Drug Sensitivity in 43 Patients During Sixteen Weeks of INH Therapy.*
The heavy black lines separate the percentages of "resistant," sensitive and negative cultures respectively.

growth as above, with the addition of ++ growth or greater in 10 microgm. of isoniazid or 100 microgm. of iproniazid per cubic centimeter. In all but 2 cases, in which significant growth appeared in the tubes containing 2.5 microgm. of iproniazid per cubic centimeter, all cultures were completely sensitive before the start of therapy. Organisms from each of these 2 patients demonstrated increasing resistance during treatment, and are included in Figure 1 in the appropriate classification.

Several important facts are indicated by these data. In the first place, bacilli with increased resistance to INH drugs appeared in a high percentage of these patients, reaching 80 per cent after fourteen weeks of treatment. Secondly, increased resistance made its first appearance as early as the third week of treatment, with the incidence increasing sharply up to the twelfth week. Finally, the patients whose cultures continued to be sensitive and those whose cultures were negative at the end of sixteen weeks of therapy were few—9.5 per cent (4 patients) and 11.9 per cent (5 patients), respectively (Table 4).

TABLE 4. *Bacteriologic and Sensitivity Status of 42 Patients at the Sixteenth Week of INH Therapy.*

Sensitivity Status		No. of Cases	Percentage	
Resistant	Slight	3	7	79
	Intermediate	14	34	
	High	16	38	
Sensitive		4	10	
Negative		5	12	
Total		42		

Correlation of Clinical Course with Emergence of Drug-Resistant Organisms

Loss of drug effect from a radiologic standpoint was considered to have occurred when either infiltration or cavity size definitely increased and, from a bacteriologic point of view, when cultures reverted to positive, or sputum bacillary count to previous levels, after an initial decline. Either one or both of these events had occurred in 28 (67 per cent) of the total of 43 patients by the sixteenth week of therapy.

Table 5 presents data on drug-sensitivity status at the time that radiologic or bacteriologic deterioration occurred in this group of patients. At this point in therapy, bacilli with increased resistance to iproniazid or isoniazid were recovered from 23 (83 per cent) of these 28 patients, 8 (29 per cent) of whom showed only "slight" resistance; the remaining 15 (54 per cent) were divided approximately equally between "intermediate" and "high" degrees of resistance.

From a clinical standpoint, the correlation with laboratory findings was often striking. Abrupt rise of the sputum bacillary count, often accompanied by enlargement of cavity, frequently followed within two weeks the first appearance of resistant organisms. Many of these patients had shown steady improvement under therapy up to this point.

Observation of individual cases yielded the distinct impression that the lesser degrees of resistance were clinically important in some. Support for this belief was afforded by the occurrence of radiologic or bacteriologic deterioration in 8 cases whose organisms had developed only slight INH resistance.

TABLE 5. *INH Sensitivity Status at Time of Bacteriologic or Radiologic Deterioration.*

Sensitivity Status		No. of Cases	Percentage	
Resistant	Slight	8	29	83
	Intermediate	8	29	
	High	7	25	
Sensitive		5	17	
Total		28		

Five patients (17 per cent) of this group showed roentgenographic or bacteriologic deterioration with bacilli still sensitive to INH. However, in contrast to those with resistant organisms, this unfavorable event was usually followed by prompt and objective evidence of improvement. Among those with resistant organisms at the time of deterioration, further improvement in chest films or bacteriologic findings was rarely observed. In spite of this, symptomatic benefit was generally maintained. An example of this situation is provided by Case 1, in which hemoptysis just before the start of isoniazid therapy was probably responsible for the evidence of increased infiltration during the second week. Two other case histories are detailed to illustrate some of these points.

Case Reports

Case 1. M. O'M., a 50-year-old nurse with a 12-year history of progressive pulmonary tuberculosis, was admitted to the sanatorium for the 3d time in July, 1950. Examination showed far-advanced disease with bilateral cavities, marked emphysema and extreme dyspnea. One cavity on the right closed after 3 months' treatment with streptomycin and PAS. The patient was otherwise unimproved, except for less dyspnea, after 19 months' bed rest, 16 months' streptomycin-PAS treatment and 14 months of pneumoperitoneum.

On January 18, 1952, isoniazid in a dosage of 4 mg. per kilogram of body weight (total of 150 mg. a day) was begun. The cavity on the left remained large. There was profuse sputum (Gaffky count of vii); bacilli were slightly resistant to streptomycin and highly resistant to PAS. Appetite and general condition were poor. The patient weighed 84½ pounds (her height was 5 feet, 4½ inches).

The clinical response is shown in Figure 2. The disease on the left increased in the 2d week but later cleared. Another increase in infiltration in the 6th week failed to clear. There was improvement in appetite and well-being and a 4½-pound weight gain in 13 weeks. The cough and the amount of sputum were markedly reduced. The sputum became Gaffky negative in the 4th week (for the first time in 18 months); resistance appeared on the 26th day, and the Gaffky count of the

sputum returned by the 11th week. Side effects included transitory numbness of the fingers and toes, anesthesia of the urethra and dizziness.

By the 16th week there was slight clinical improvement with gradual regression to the status before treatment. The patient

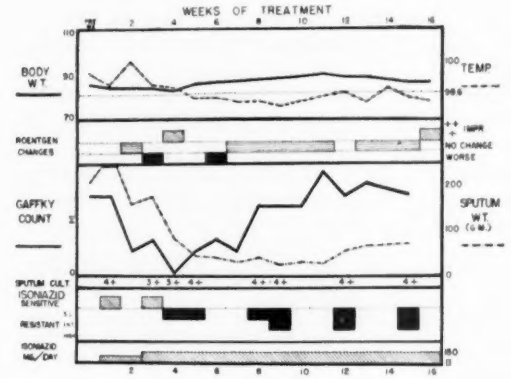

FIGURE 2. *Clinical Data during Sixteen Weeks of INH Therapy in Case 1.*

was bacteriologically improved and radiologically slightly worse. Bacilli showed intermediate resistance to isoniazid.

This case illustrates early emergence of drug-resistant organisms in a patient with extensive caseocavitary disease. Appearance of organisms with only "slight" resistance to isoniazid was shortly followed by reversion of sputum bacillary counts to initial levels after a period of definite benefit. Radiographically, this patient showed progression of disease (during the third week of treatment), which then cleared rapidly; this was regarded as possibly representing extension that had occurred during a hemoptysis immediately before the start of therapy. A second increase in infiltration appeared during the sixth week and failed to clear significantly.

Case 2. A. M., a 26-year-old woman, had had bilateral, cavitary pulmonary tuberculosis for 4 years that had progressed on home care and intermittent streptomycin and PAS. In May, 1951, she was admitted to the sanatorium with multiple cavities and in poor condition. There was no improvement on 9 months of bed rest, 7 months of continuous streptomycin and PAS and 5 months of pneumoperitoneum.

On January 18, 1952, iproniazid (4 mg. per kilogram of body weight to a total of 150 mg. a day) was begun. There was a moderate amount of cough and sputum, which had a Gaffky count of ix. The bacilli were highly resistant to streptomycin and PAS. The patient weighed 93 pounds (her height was 5 feet), and was in poor general condition.

The clinical response is shown in Figure 3. There was a marked increase in appetite, strength and well-being, with a 25-pound weight gain in 9 weeks. Cough and sputum weight were markedly reduced and the Gaffky count declined to ii in the 7th week; bacterial resistance appeared on the 49th day, with increased infiltration in the chest film during the 10th week. Cough increased and appetite was less in the 11th week. After the appearance of drug-resisting organisms, the Gaffky count returned to x by the 11th week. Side effects included transitory skin rash and mild muscle twitching.

At the end of the 16th week the patient's general status was much improved, but the tuberculosis was worse. There was a beginning return of symptoms. Bacilli were highly resistant to iproniazid.

This patient showed a striking response in all respects to INH therapy. Deterioration during the 8th to 12th weeks of treatment was therefore conspicuous and, from a radiographic standpoint, was coincident with the appearance of organisms with

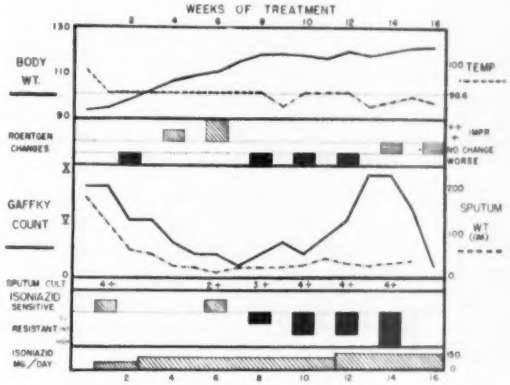

FIGURE 3. *Clinical Data during Sixteen Weeks of INH Therapy in Case 2.*

only slight increase in resistance to INH, and bacteriologically with a reversion of sputum bacillary counts to previous high levels.

Case 3. A. Q., a 34-year-old man, had a 17-year history of progressive far-advanced pulmonary tuberculosis. Thoracoplasty had been performed on the right in 1939. Cavitary disease had been present on the left since 1948. There was no improvement with streptomycin and tibione.

On May 20, 1950, the patient was admitted to the sanatorium with multiple cavities of the left apex. He failed to im-

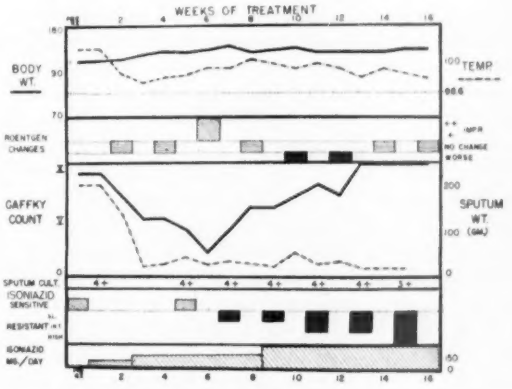

FIGURE 4. *Clinical Data during Sixteen Weeks of INH Therapy in Case 3.*

prove on bed rest for 20 months, pneumoperitoneum for 8 months and Monaldi drainage, streptomycin and PAS, terramycin and oxygen for 8 months.

On January 18, 1952, isoniazid (4 mg. per kilogram of body weight for a total of 250 mg. a day) was begun. Multiple cavities of the left upper lobe persisted. There was profuse sputum (Gaffky count of ix); the bacilli were highly resistant to strep-

tomycin and PAS. Appetite and general condition were fairly good, although marked dyspnea was present.

The clinical response is shown in Figure 4. A clear-cut reduction in cavity size occurred in the 6th week but the cavity returned to its pretreatment size by the 12th week. There was a slight increase in appetite and well-being and a weight gain of 4 pounds in 12 weeks. The cough and amount of sputum were markedly reduced. The Gaffky count fell to ii in the 6th week during which drug-resistant organisms appeared, and rose to viii by the 11th week. Side effects included hyperreflexia, insomnia and paresthesias. In the 15th week a severe purpuric rash appeared on the lower extremities, associated with hemoptysis, necessitating discontinuance of treatment. Therapy was later resumed without serious recurrence.

At the 16th week the patient was practically unimproved except for less cough and expectoration. The bacilli were highly resistant to isoniazid.

The data in this case demonstrate a clear-cut loss of drug effect both radiographically and bacteriologically approximately three weeks after the first appearance of INH-resistance. At the time these unfavorable events occurred, bacilli obtained from the sputum were showing intermediate resistance to isoniazid.

Discussion

Although clinical improvement under therapy with isoniazid and particularly iproniazid used alone is striking, the rapid emergence of resistant organisms and their clinical implications in this group of patients indicate the importance of drug-sensitivity studies for evaluation of antituberculosis agents. Once again, the case selection for the present study must be emphasized. Patients were deliberately chosen as those most likely to provide continuing positive sputum for bacteriologic study, the resultant group being composed largely of patients with chronic, advanced, cavitary tuberculosis. If streptomycin alone had been used in such a group, resistant organisms would likewise have appeared rapidly and consistently. Greater INH effectiveness in more recent disease was demonstrated in a most interesting way by prompt closure of relatively new cavities in 2 patients whose old cavities remained unchanged during therapy.

The magnitude of the problem of increased bacillary resistance to INH in these patients may be appreciated if one recalls that 80 per cent of the whole group exhibited organisms with increased resistance to INH by the end of fourteen weeks of therapy. These results compare fairly closely with those in similar groups reported elsewhere.[10-12, 14, 15] Furthermore, data available on some of these patients up to six months after treatment was discontinued, indicate that resistance to the INH drugs persists after termination of treatment, unlike the often transient nature of resistance to PAS.

Experience with this group of patients appears to confirm the impression that the emergence of INH-resistant organisms has important clinical implications. This is shown not only by the absence of radiographic or bacteriologic improvement in most patients with drug-resistant organisms but also by actual deterioration in a high percentage. As in the early days of streptomycin treatment, onset of bacterial resistance was often associated with bacteriologic relapse and with enlargement of cavity. Similar reports of frequent relapse during isoniazid therapy, associated with the appearance of INH-resistant organisms, are now accumulating rapidly.[14-19]

From a practical standpoint, the level of increased bacillary resistance to INH that results in loss of drug effect clinically is of considerable importance. Evidence that small degrees of bacterial resistance to INH are often significant may be summarized as follows:

Cases of abrupt rise in sputum bacillary counts, often accompanied by unfavorable roentgenographic change, occurred in 8 patients after the emergence of bacilli with only "slight" INH resistance.

Analysis of individual cases reveals a close time relation in many cases between development of slight degrees of bacterial resistance to INH and occurrence of deterioration.

With few exceptions, significant bacteriologic or radiologic improvement failed to occur after organisms with any degree of increased drug resistance had appeared in the sputum.

It is interesting that general clinical condition did not, as a rule, follow the pattern of the more objective radiographic and bacteriologic deterioration. Weight gain and sputum decrease, in particular, were often maintained in spite of actual progression in the chest film, and of reversion of bacillary counts to high levels. By the end of six months of therapy, although most patients with initial benefit had reverted to their status before treatment so far as radiograph appearance and bacteriology were concerned, general clinical status was usually definitely improved over that at the start of therapy. Such an improvement is often of considerable value, even though more lasting benefit on the disease is not anticipated.

The frequency and clinical significance of the emergence of bacterial resistance in this group emphasizes the limitations of INH drugs when employed alone in this type of case. When planning therapy, one should give careful consideration to early measures for collapse or excision of cavities, since there is evidence that, as when streptomycin is used alone, persistence of sources of multiplying bacilli will lead to rapid emergence of drug-resistant organisms and consequent loss of drug effectiveness. Combinations of either isoniazid or iproniazid with other agents are currently under study at this institution and elsewhere, and observations to date indicate that their usefulness will be considerably

extended by virtue of the postponement or prevention of the emergence of resistance.[11-13,15]

Summary

The clinical course of 43 patients under treatment with the hydrazides of isonicotinic acid (27 on isoniazid and 16 on iproniazid) was studied with particular attention to its relation to the emergence of drug-resistant tubercle bacilli.

The patients represented a selected group of predominantly far-advanced cases of chronic, cavitary tuberculosis.

Emergence of increased bacterial resistance to isoniazid or iproniazid appeared as early as the fourth week of therapy, and by the fourteenth week 80 per cent of the group yielded cultures showing increased resistance in vitro.

Loss of drug effect, as indicated by reversion of sputum bacillary counts to previous high levels, or by unfavorable radiographic changes, occurred during therapy in 28 of 43 patients. In most cases such an event was preceded by, or coincident with, the appearance of drug-resistant organisms in the sputum.

Results in this group of patients suggest that the appearance in the sputum of bacilli with only slight degrees of increased drug resistance may be associated with roentgenographic or bacteriologic evidence of loss of drug effect.

General clinical improvement, which was striking in most cases, was often maintained in spite of radiographic or bacteriologic deterioration.

Isoniazid drugs in this type of case may be of use in conjunction with collapse or excision of cavitary disease, and in combination with other chemotherapeutic agents.

References

1. Robitzek, E. H., and Selikoff, I. J. Hydrazine derivatives of isonicotinic acid (rimifon marsilid) in treatment of active progressive caseous pneumonic tuberculosis. *Am. Rev. Tuberc.* **65**:402-428, 1952.
2. *Idem.* Tuberculosis chemotherapy with hydrazine derivatives of isonicotinic acid. *Dis. of Chest* **21**:385-438, 1952.
3. Steenken, W., Jr., Meade, G. M., Wolinsky, E., and Coates, E. O., Jr. Demonstration of increased drug resistance of tubercle bacilli from patients treated with hydrazines of isonicotinic acid. *Am. Rev. Tuberc.* **65**:754-758, 1952.
4. Tempel, C. W., Pitts, F. W., Miller, F. L., Dye, W. E., and Fitzpatrick, M. J. Unpublished data.
5. Goulding, R., King, M. B., Knox, R., and Robson, J. M. Relation between in-vitro and in-vivo resistance to isoniazid. *Lancet* **2**:69, 1952.
6. Morelli, E., and Daddi, G. La resistenza acquisita dei B. di Koch all' isonicotinilidrazide. *Lotta contro tubere.* **22**:397-399, 1952.
7. Tanner, E., Wanner, J., Wehrlin, H., and Ramer, Z. Rimifon in der Behandlung der Tuberkulose: erste klinische Beobachtungen. *Schweiz. Ztschr. Tuberk.* **9**:255-266, 1952.
8. Bowen, D. A. L., and Collins, D. M. Development of drug resistance to isoniazid in cases of pulmonary tuberculosis. *Tubercle* **33**:276-278, 1952.
9. Petit, A. Preliminary note on appearance of resistance to isonicotinic acid hydrazide. *Scalpel* **105**:1131, 1952.
10. Treatment of pulmonary tuberculosis with isoniazid. (Interim Report to the Medical Research Council by their Tuberculosis Chemotherapy Trials Committee.) *Brit. M. J.* **2**:735-746, 1952.
11. Dye, W. E., Lynch, H. P., and Brees, A. G. Incidence of bacterial resistance encountered with tuberculosis chemotherapy regimens employing isoniazid alone and in combination with intermittent streptomycin. *Am. Rev. Tuberc.* **67**:106, 1953.
12. Consolidated tables. In *Proceedings of the 12th Veterans Administration, Army-Navy Conference on the Chemotherapy of Tuberculosis, February, 1953.* (In press.)
13. United States Public Health Service Study of INH — present status. In *Proceedings of the 12th Veterans Administration, Army-Navy Conference on the Chemotherapy of Tuberculosis, February, 1953.* (In press.)
14. Foreign Letters. Japan. Experiments with isonicotinic acid hydrazid. *J. A. M. A.* **150**:50, 1952.
15. Joiner, C. L., et al. Isoniazid in pulmonary tuberculosis: its use with and without streptomycin. *Lancet* **2**:843-849, 1952.
16. Nash, J. C., and Grosfeld, W. Isoniazid and iproniazid resistance in pulmonary tuberculosis. *J. A. M. A.* **150**:813, 1952.
17. Foreign Letters. Denmark. Treatment of pulmonary tuberculosis with isonicotinic acid. *J.A.M.A.* **150**:49, 1952.
18. Witkind, E., and Willner, I. Clinical experiences with isonicotinic acid hydrazide in tuberculosis. *Dis. of Chest* **23**:16-27, 1953.
19. Omodei-Zorini, A. L'expérience de l'institut "Carlo Forlanini" sur une nouvelle préparation chimiothérapique: antituberculeuse: l'hydrazide de l'acide iso-nicotinique. *Lotta contro Tubere.* **22**:400-412, 1952.

ELASTIC STOCKINGS IN THE PREVENTION OF PULMONARY EMBOLISM*
II. A Progress Report

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BOSTON

IN a recent study it was found that the incidence of pulmonary embolism was reduced in hospital patients who wore elastic stockings as compared with those who wore nonelastic stockinette throughout their hospital stay.§ The explanation offered was that there was an increase in *linear velocity* (not in volume) of blood flow in the leg veins of those who wore elastic stockings. The acceleration of flow was assumed to result from a reduction in the caliber of the veins when they were compressed by the elastic stockings. This acceleration of venous flow supposedly lessened the tendency to phlebothrombosis in the legs, where it is known to originate in many cases of pulmonary embolism.

The differences observed in the two groups were statistically significant but were nevertheless considered inconclusive, both because the incidence of pulmonary embolism in general-hospital patients is low and because in many cases the diagnosis can be made conclusively only with autopsy evidence. Therefore, it was decided to continue to study the prophylactic value of elastic stockings against pulmonary embolism, but this time as a routine, not

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§Wilkins, R. W., Mixter, G., Jr., Stanton, J. R., and Litter, J. Elastic stockings in prevention of pulmonary embolism: preliminary report. *New Eng. J. Med.* **246**:360-364, 1952.

an alternate-case, procedure. It was believed that this not only would provide more cases in less time but also would shed light on the feasibility and effectiveness of the method as a standard hospital practice.

Method

In the interval between the termination of the alternate-case study and the beginning of the routine study a period of ten months elapsed during which no stockings of any kind were used (except in a few private patients for whom elastic stockings were prescribed by the physician in charge). This interval then served as a control period for the succeeding routine (as well as the preceding alternate-case) study. The clinical and postmortem observations made before (during the alternate-case study) and afterward (during the routine study) were carried out during this ten-month interval. Thus, control data were obtained on 6090 admissions, in 4450 of which the patients were in the hospital for over twenty-four hours, were more than twenty years of age and were comparable in all ways to the cases observed during the preceding and following studies on the use of elastic stockings.

The study was then resumed with the routine application of elastic stockings to *all* patients over twenty years of age admitted to the hospital for over twenty-four hours. This was carried out with the aid of a full-time nurse-technician* who provided each patient on admission with a correctly-fitting pair of special bed-wear, knee-length stockings.† The stockings were worn by the patients continuously throughout their hospital stay except when they were bathing or changing their stockings for a fresh pair. A note was made on the chart each morning concerning whether the stockings were being worn.

Table 1. *Reasons for Not Wearing Stockings.**

Reason	No. of Cases
Ulcers of one or both legs	41
Traction, casts, deformities or amputations	59
Vein ligation or stripping	39
Vascular disease, gangrene or vascular disease and diabetes	73
No pulses palpable below femoral arteries	58
Patient refusal or doctor's permission to remove	45
Thromboembolic disease on admission	31
Pulmonary edema and marked peripheral edema	16
Edema without palpable pulses	10
Local infections, skin grafts or contusions	69
Total	441*

*Of these 441 cases, 92 wore one stocking. The total number who wore no stockings was thus, 349.

During this period of twelve months 7296 patients were admitted to the hospital, of whom 5467 were available for study. All types of patients, medical, surgical and obstetric, wore the stockings except for 349 (6.3 per cent) who could not (or would not) wear them. Table 1 shows the reasons why this group of patients did not wear elastic stockings. These cases were nevertheless included in the study and the patients regarded merely as persons in whom the method failed to be applicable.

In the ten-month interval control period there were 189 deaths from all causes and 103 autopsies (54 per cent), whereas during the ensuing twelve-month study period there were 178 deaths and 99 autopsies (55 per cent). All autopsies during both periods were reviewed, and in the cases with any evidence suggesting pulmonary embolism (with or without infarction) it was decided whether pulmonary embolism was the direct cause of death ("fatal") or not the direct cause of death ("nonfatal"). In the latter group after review of the clinical and pathological data it was further decided whether embolism was possibly contributory to death ("contributory") or definitely not contributory ("incidental").

In the "fatal" cases it was usually easy to make a decision since there was unequivocal autopsy evidence of a massive pulmonary embolism. When there was any doubt that pulmonary embolism was the direct cause of death, a diagnosis of "nonfatal" pulmonary embolism was made. In most "nonfatal" cases it was also easy to make a decision since it was obvious that the embolism definitely contributed to the patient's death. However, in some nonfatal cases decision was difficult because although embolism might be deemed important it was considered only "possibly" contributory to death. Nevertheless, in all such doubtful cases the diagnosis of "contributory" nonfatal pulmonary embolism was made rather than "incidental" pulmonary embolism. Thus, only cases in which pulmonary embolism though present clearly could have played no role in the fatal course were diagnosed as "incidental."

Table 2. *Relation of Pulmonary Embolism to Death.*

Period	Total Cases Studied	"Fatal" Cases	"Nonfatal" Cases	
			Contributory	Incidental
Control interval...	4450	7	10	4
Study period.....	5467	3	5	4

Results

Table 2 shows that the incidence of "fatal" and contributory "nonfatal" cases of pulmonary embolism proved at autopsy was approximately halved when elastic stockings were "routinely" used in this hospital. Thus, there were only 3 cases of fatal pulmonary embolism during the study period as compared with 7 in the control interval. Only 1 of these 3, however, can be regarded as an

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actual failure of stockings. This death from "massive" pulmonary embolism occurred in an eighty-four-year-old man ten days after a colectomy for carcinoma. Careful dissection of the veins revealed no thrombi in the calves or thighs, although thrombi were present in the prostatic plexus and presumably had extended to the pelvic veins and resulted in an embolism. The second fatal case was that of a forty-eight-year-old man with rheumatic heart disease and marked congestive heart failure who entered the hospital with phlebothrombosis and pulmonary infarction of which he died four days later. Since the stockings could not conceivably have prevented the phlebothrombosis in this case they cannot be said in the strict sense to have failed their purpose. The third case was that of a fifty-six-year-old woman with carcinomatosis originating in the stomach who died of massive pulmonary embolism two days after gastrectomy. However, with her physician's permission, she had not worn elastic stockings at any time.

It is also interesting that only 2 of the 5 patients in the "contributory" and only 1 of the 4 in the "incidental" nonfatal cases during the stocking study actually wore the elastic stockings. Nevertheless, all these cases of pulmonary embolism proved at autopsy were regarded as failures of the method. Thus, there were a total of 12 cases of pulmonary embolism proved at autopsy out of 5467 patients studied during the period when an attempt was made to apply elastic stockings routinely. However, this compares favorably with the 21 cases out of 4450 patients followed in the interval control period, since it shows that the incidence of all forms of pulmonary embolism, "fatal" and "nonfatal," was halved during the routine stocking study.

Discussion

This study confirms and enlarges the experience gained in the previous study. In that series, 5426 patients were included, half of whom were assigned at random to the test group and the other half to the control group. Among those who wore elastic stockings there were no "fatal" cases of pulmonary embolism whereas among comparable control cases there were 2 "fatal" cases proved at autopsy. However, there were 685 "out of series" patients (12.6 per cent) who could not or would not have worn elastic stockings even if assigned to the group. Among these "out of series" cases there were 4 of "fatal" pulmonary embolism. Since only half of them may be considered as having really belonged to the control group, the total number of "fatal" cases among the 2713 control patients may be said to have been 4. This is about the same incidence of "fatal" pulmonary embolism as occurred during the ten-month interval control period when no stockings were used.

The incidence of "nonfatal" pulmonary embolism was also about the same among the "control" cases of the previous alternate-case study as among the "control" cases of the ten-month interval period. Thus, if one assigns half the "out of series cases" in the alternate-case study to the control group, there were in all 7 "nonfatal" cases among 2713 patients as compared with 15 "nonfatal" cases among 4450 interval patients.

There is an important distinction to be drawn between the present routine study and the previous alternate-case study — namely, that in the present study no cases were considered "out of series." That is to say, all cases were included, and all patients who could possibly wear elastic stockings were so equipped. As a result only 6 per cent (as compared with 12.6 per cent in the alternate-case study) wore no stockings. Even these, however, were regarded in the analysis of results as "in series"—that is, being subject to the method. It is our impression that as the routine practice of wearing elastic stockings in this hospital has continued, fewer and fewer patients are failing to wear them. This is due in part to acceptance by the patient but perhaps is due more to the realization on the part of physicians that at least the stockings do no harm, and apparently do considerable good. In this connection it is interesting that as this article is being written we have just passed the 3000th additional patient since the end of the study reported in this paper, and ironically have just had our first additional "fatal" case of pulmonary embolism proved at autopsy. This occurred in an enormously obese woman one week after the surgical repair of an umbilical hernia. During this week she hardly moved in bed, and never got out of it. Although the possibility of phlebothrombosis was considered to be great in this patient, she was not treated by either anticoagulants or venous ligation, because she never had any positive clinical evidence of the disease. She died suddenly of a massive pulmonary embolus getting out of bed the first time. Even so, including this case, our incidence of "fatal" pulmonary embolism is running lower than a year ago.

This case also serves to emphasize again that stockings cannot be expected to prevent all cases of pulmonary embolism, even all those originating in the lower limbs. Indeed, they are presumably of no value, and conceivably might do harm, when definite thrombophlebitis or phlebothrombosis is already present. This should be treated by anticoagulants with or without venous ligation. The chief purpose of the stockings is to help *prevent* the formation of deep-calf thrombosis, and so to lessen the likelihood of proximal propagation of clots into the larger veins, with danger of embolization. Obviously, they can have no influence on thrombosis originating in the thigh, pelvis, arms or heart itself. Therefore, if they are to be used, they

must be applied routinely to all patients (except when definitely contraindicated), without influencing the regular treatment of known or suspected phlebothrombosis or thrombophlebitis. Despite this fact, it is our impression that the use of anticoagulants and prophylactic venous ligation in this hospital has decreased markedly in the past year, during which stockings have been applied routinely. Although this makes the favorable results reported here more impressive, it is not a desirable situation, since it denotes an unwarranted dependence on the elastic-stocking method, which should be regarded as an adjunct to, not a substitute for, the other measures designed to lessen the incidence of fatal pulmonary embolism. Thus, to prevent phlebothrombosis, muscular exercise, especially early and effective ambulation, should be used if possible along with elastic stockings to speed venous flow, whereas anticoagulants should be used, especially in highly susceptible patients, to lessen the coagulability of the blood. Finally, whenever venous thrombosis is suspected or known to be already present anticoagulants with or without venous ligation should be considered the treatment of choice.

Summary and Conclusions

Elastic stockings routinely applied to hospital patients over twenty years of age reduced by about half the expected incidence of fatal pulmonary embolism in a series of 5467 medical, surgical and obstetric patients.

Every type of hospital patient may safely wear elastic stockings except those with severe local disease in the legs, such as ischemia, inflammation or trauma.

Elastic stockings are not a substitute for but an addition to, measures designed to prevent pulmonary embolism, such as anticoagulants and venous ligation. They apparently prevent venous thrombosis in the calves and, through this effect, reduce the incidence of embolism.

The results of the method warrant its consideration as a routine hospital procedure.

CARE OF THE PREMATURE INFANT IN MASSACHUSETTS

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BOSTON

PREMATURITY is recorded as the primary or contributory cause of death on approximately 50 per cent of the death certificates of infants dying under one year of age in Massachusetts. In 1951 more than 1000 infant deaths were recorded as being associated with prematurity.

The following study considers the efforts of the Commonwealth of Massachusetts to reduce the number of deaths from this cause. The historical background is presented along with an analysis of the problem based on the available statistics for the year 1951.

Historical Background

The physicians of Massachusetts, the Department of Public Health and the people of the Commonwealth (as represented by the Legislature) early recognized the importance of prematurity as a major factor in infant mortality. The contributions of Massachusetts physicians to the clinical management of prematurity are well known. Less well known is the help and stimulation certain outstanding pediatricians and obstetricians provided the Department in developing one of the first state programs for the care of premature infants.

This program helped physicians and nurses to obtain training in the care of the prematurely born infant, enabled certain hospitals to become "centers" for the care of premature infants and devised incubators for the care and transportation of premature infants. These incubators were simple in design and easy to construct. Today they appear crude. However, when one considers that at the time they were built certain hospitals used incubators for the infant's body only and left his head outside, the incubators are seen to have been relatively efficient.

The Massachusetts Legislature, in 1937, became aware of the importance of prematurity as a factor in infant mortality and passed a law providing for the hospital care and transportation of premature infants. When parents were unable to pay, the costs were made the responsibility of the local boards of welfare. The Act stated that families who were recipients of such aid should not be regarded as "on welfare." Thus, it was recognized that the birth of a premature infant to a family in the low-income group can result in economic and social hardship. The act also provided that the births of all infants weighing 5 pounds or less at birth be reported to local boards of health and local boards of welfare.

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In an epidemiologic approach to the problem, the Department of Public Health requested copies of these reports from the local boards of health. Reporting was incomplete; in the six-year period 1943–1948 inclusive, only 1570 reports were received.

In 1949 the Legislature, at the request of a special commission appointed to study and investigate certain public-health matters, again considered the status of the premature infant and wrote into the law an act that made the costs of hospital care of certain premature infants (those weighing 4½ pounds or less at birth whose parents were unable to pay for the care) the responsibility of the local board of health of the city or town in which the mother resided. It also made the Department of Public Health responsible for the payment for hospital care of certain infants (as defined above) whose parents did not have legal settlement in any city or town in Massachusetts. Thus, the Legislature recognized that prematurity is a health and not a welfare matter. The same act requires the reporting of the births of all infants weighing 5½ pounds or less at birth to the local boards of health. This legislation is unique; it is based on the New England tradition of city and town home rule. In 1951 the local boards of health spent $140,000 on the hospital care of premature infants in accordance with this act, and the Department spent $16,000 on unsettled cases. Approximately 25 per cent of all families of premature infants weighing 4½ pounds or less at birth received assistance in meeting the costs of hospital care.

The present program of the Department, which is aimed at reducing the mortality from prematurity, has three components — education, service and research. Women are urged to seek medical care from their physicians as soon as they know they are pregnant. The physician can do little to correct abnormal medical and social conditions that cause prematurity if he sees the patient for the first time in the last trimester of her pregnancy. The Department, with the co-operation of the Children's Bureau, offers advanced courses to physicians and nurses on the care of the premature infant. The Department also conducts seminars in different areas of the State and supplies speakers for hospital staff meetings to discuss the obstetric factors in prematurity.

The Department licenses hospitals. This act of licensure helps ensure the mother a safe environment in which to have her baby, the physician an adequate case room in which to work and an adequate nursery in which to care for the premature infant. The Department also offers medical and nursing consultation services to hospital obstetric and nursery units. Medical, public-health-nursing and social-service consultations are made available to local boards of health to help them carry out their responsibilities under the act of 1949.

Research in this field has been confined to the analysis of reports to obtain data on the incidence of, and the mortality from, prematurity — that is, a study of the epidemiology of prematurity on which a more effective program of prevention and treatment may be based. The rest of this paper deals with an analysis of the statistical data that the Department has accumulated.

Source of Material

Because Massachusetts is the only state in the Union in which birth weight is not recorded on the birth certificate, data on premature births must be obtained from other sources. The two sources used are the annual hospital reports and reporting of premature births as required by law.

The first of these are submitted to the Department by every maternity hospital in the State. These reports do not identify individual infants and do not give information by weight groups under 4½ pounds. Among the items reported are the number of premature births by sex, color and plurality of birth, the number of premature infants born elsewhere and admitted to the hospital for care, and the number of deaths occurring among such infants in the maternity section of the hospital. No information is available on deaths that occur after the infant leaves the hospital or after it is transferred from the maternity to the pediatric section of the hospital.

The other source of data available is the reporting of prematurity as required by Chapter 601, of the *Acts* of 1949. This consists of reports of individual premature births made out in duplicate by the hospital and sent to the board of health of the city or town of the mother's residence. The carbon copy is then sent to the Department. These reports contain information on place of mother's residence, place of delivery, hospital to which infant was transferred for care, birth weight, plurality of birth, sex and color. These reports are matched with neonatal death certificates to obtain information on deaths among premature infants.

The Department received 5348 reports of premature infants born alive in 1951; 5211 were in maternity hospitals, 76 were born in other hospitals, and only 61 were reported as being born at home. Of the total, 2522 (47.2 per cent) were males and 2826 (52.8 per cent), were females. There were 4438 (83 per cent) single births and 910 (17.0 per cent) plural births.

Completeness of Reporting

The validity of conclusions drawn from this material depends upon the completeness of reporting. Because the information the hospitals are required by law to report on each infant is more detailed than that contained in the annual hospital reports, data obtained from the former should be of more value for statistical analysis. However, a

comparison of the two sources shows that the annual hospital reports listed 6491 premature infants born in Massachusetts maternity hospitals in 1951, whereas from the same hospitals only 5211 individual reports of premature births (80 per cent) were received. Therefore, in this analysis, we have used the annual hospital reports as the standard.

TABLE 1. *Completeness of Reporting of Premature Infants Born in Maternity Hospitals (Massachusetts and Each Health District, 1951).*

PLACE OF BIRTH (BY HEALTH DISTRICT)	NO. OF INFANTS REPORTED ON ANNUAL HOSPITAL REPORTS	REPORTS RECEIVED BY DEPARTMENT	
		NO.	PERCENTAGE*
Southeastern	700	508	73
South Metropolitan	562	441	78
North Metropolitan	2507	2224	89
Northeastern	736	578	79
South Central	580	452	78
North Central	469	382	81
Connecticut Valley	736	512	70
Berkshire	201	114	57
Totals	6491	5211	
Average			80

*The percentages are based on the number of premature births in specified group reported on the annual hospital reports.

There are probably some errors in these reports — we have not checked the accuracy of all of them. When there were obvious discrepancies the hospitals were queried, and the necessary corrections made. The incidence of prematurity as determined from these reports is comparable to that reported from New York State.

FIGURE 1. *Completeness of Reporting of Premature Births by Health Districts in Massachusetts in 1951.*

There was a variation in the completeness of reporting of individual births by the maternity hospitals in the 8 districts (Table 1 and Fig. 1). The most incomplete reporting was by the hospitals in the Berkshire Health District (57 per cent), and the most complete was by the hospitals in the North Metropolitan District (89 per cent), in which the large metropolitan hospitals are located.

When the hospitals of the State are grouped according to the number of live births in 1951 the variation in completeness of reporting is directly related to the size of the hospital. The reporting from the large hospitals is much better than that from the small hospitals. The hospitals with less than 500 live births sent in reports on 70 per cent, those with 500 to 999 live births 79 per cent, and the large hospitals with 1000 or more live births 84 per cent of the premature births occurring in their obstetric units.

Individual reporting is less complete for the heavier infants. Reports on only 73 per cent of the premature infants with a birth weight of more than 2000 gm. (4 pounds, 6 ounces) were received by the Department as compared with 93 per cent of those weighing less than 2000 gm. The reporting of the small infants is more complete, not only for the State as a whole but also for each health district.

The more complete reporting of premature infants with lower birth weights is probably directly related to the fact that the law provides, under certain circumstances, for financial assistance to the parents of infants weighing 4½ pounds (2040 gm.) or less at birth. This assistance can only be made if the birth is reported within a given time.

The less complete reporting of the infants weighing more than 2000 gm. is probably due to the fact that some confusion still exists regarding the definition of a premature infant. The earlier law required the reporting of infants weighing 5 pounds (2270 gm.) or less at birth, whereas Chapter 601 of the *Acts* of 1949, in accordance with the international definition of a premature infant, requires the reporting of infants weighing 5½ pounds (2500 gm.) or less at birth.

TABLE 2. *Total Live Births and Premature Live Births in Maternity Hospitals (Massachusetts and Each Health District, 1951).*

HEALTH DISTRICT	NO. OF LIVE BIRTHS	NO. OF PREMATURE LIVE BIRTHS*
Southeastern	9,540	700 (7.3%)
South Metropolitan	8,728	562 (6.4%)
North Metropolitan	37,091	2507 (6.8%)
Northeastern	12,249	736 (6.0%)
South Central	8,655	580 (6.7%)
North Central	7,068	469 (6.6%)
Connecticut Valley	10,703	736 (6.9%)
Berkshire	3,100	201 (6.5%)
Totals	97,134	6491 (6.7%)

*The percentages are based on the total live births in specified group.

INCIDENCE OF PREMATURITY

The most reliable information on the incidence of prematurity appears to be the annual hospital reports. Since more than 98 per cent of the births in Massachusetts occur in hospitals, totals from this source should be close to the total incidence.

Table 2 shows that 6.7 per cent of the living infants in Massachusetts hospitals in 1951 weighed 5½ pounds or less at birth. This incidence varied among the different districts from 6.0 per cent for the hospitals in the Northeastern Health District to 7.3 per cent for the hospitals in the Southeastern Health District.

There were 137 maternity hospitals in Massachusetts in 1951. During that year in these hospitals 6491 premature births occurred, of which 52 per cent were in the 29 hospitals with 1000 or more live births per year, 35 per cent in the 48 hospitals with 500 to 999 live births and 13 per cent in the 60 hospitals with less than 500 births. This is similar to the percentage distribution of the total live births occurring in these hospitals.

The incidence of prematurity as recorded in the annual hospital reports was higher among females (7.4 per cent) than among males (6.0 per cent), higher for nonwhite (10.0 per cent) than for white (6.0 per cent) and much higher among plural (49.1 per cent) than among single births (5.8 per cent).

Premature Births by Birth Weight

Because the hospital reports do not separate birth weight into categories below 4 pounds, 8 ounces (2040 gm.), the only source of information on the number of infants in the groups below 2000 gm. must come from the individual premature birth reports. Since the reporting is only 80 per cent complete and the completeness of reporting varies with birth weight and hospital size, the limitations of the data must be kept in mind in the interpretation of the following material.

The distribution by birth weight is shown in Table 3. Of the total premature infants reported to the Massachusetts Department of Public Health, 62 per cent weighed more than 2000 gm. If the reporting had been complete, this percentage would probably have been higher since the reporting of the larger premature infants was less complete than that of the smaller ones. There was a much higher proportion of premature infants in the low-weight groups among plural births than among the single births. Sixty-four per cent of the infants in the single premature births weighed more than 2000 gm. as compared with 52 per cent of those in the plural premature births. There was also a higher proportion in the low-weight groups among the male than among the female premature infants.

Neonatal Deaths among Premature Infants

The individual reports are sent to the local boards of health shortly after the birth of the premature infant. From these reports there is no way of knowing whether the infants survived the neonatal period. The reports are therefore matched with the death certificates of all neonatal deaths (under twenty-eight days) to obtain information regarding deaths among premature infants.

Included in our study are 83 premature infants who died but whose death certificates did not mention prematurity, which the attending physician did not regard as a contributing factor. Since the death certificates do not always mention prematurity and since the reporting of premature births is only 80 per cent complete, there is no way of knowing exactly how many deaths occurred in Massachusetts among prematurely born infants.

Table 3. *Premature Infants by Birth Weight, Sex and Plurality of Birth (Massachusetts, 1951).*

Birth Weight*	Total Premature Births	Single Premature Births			Plural Premature Births		
		Total	Male	Female	Total	Male	Female
gm.							
1000 or less	421 (8.0%)	334 (7.6%)	170 (8.3%)	164 (7.0%)	87 (9.7%)	53 (12.0%)	34 (7.5%)
1001–1500	465 (8.8%)	373 (8.5%)	182 (8.9%)	191 (8.2%)	92 (10.3%)	55 (12.4%)	37 (8.1%)
1501–2000	1118 (21.2%)	870 (19.9%)	425 (20.8%)	445 (19.0%)	248 (27.6%)	111 (25.1%)	137 (30.1%)
2001–2500	3277 (62.0%)	2807 (64.0%)	1267 (62.0%)	1540 (65.8%)	470 (52.4%)	223 (50.5%)	247 (54.3%)
All weight groups	5281†(100%)	4384 (100%)	2044 (100%)	2340 (100%)	897 (100%)	442 (100%)	455 (100%)

*The equivalent weights in pounds and ounces are as follows:
1000 gm. or less — 2 lb., 3 oz., or less.
1001–1500 gm. — 2 lb., 4 oz.,–3 lb., 4 oz.
1501–2000 gm. — 3 lb., 5 oz.,–4 lb., 6 oz.
2001–2500 gm. — 4 lb., 7 oz.,–5 lb., 8 oz.

†The Massachusetts Department of Public Health received 5348 premature reports for 1951; 67 of these reports are omitted because birth weight was not recorded.

Table 4. *Premature Births and Neonatal Deaths among Premature Infants by Birth Weight (Massachusetts, 1951).*

Birth Weight	Premature Births	Deaths Under Twenty-Eight Days of Age	
		No.	Mortality
gm.			%
1000 or less	421	395	93.8
1001–1500	465	269	57.8
1501–2000	1118	206	18.4
2001–2500	3277	155	4.7
Not reported	67	52	77.6
Totals	5348	1077	
Average			20.1

In matching the death certificates with the reports of premature births we found that there were 399 death certificates that gave prematurity as the primary or the contributory cause of death and yet the premature birth had not been reported to us. Evidently, many infants who died were not reported at birth. We therefore sent letters to 115 hospitals requesting information on birth weight on these 399 infants. Replies were received from all but 1 hospital. Information was given on 387 infants. In 25 cases the infants weighed more than 5½ pounds at birth; the remaining 362 weighed 5½ pounds or less at birth. These 362 premature births have been included in our study; indeed they constitute about a third of the total neonatal deaths among premature infants in our statistical material. The fact that so large a proportion of all deaths associated with prematurity would never have been discovered by a tracing of the prematurely born infants reported is striking testimony to the need for better reporting.

The following figures are based on the 1077 neonatal deaths that occurred among the 5348 premature infants in our study. One out of every 5 premature infants fails to survive the first month of life. This proportion varied according to the birth weights of the infants (Table 4). The smaller the infants, the poorer their chances for survival; 94 per cent who weighed 1000 gm. or less, 58 per cent of those weighing 1001 to 1500 gm., 18 per cent of those weighing 1501 to 2000 gm., and 5 per cent of those weighing more than 2000 gm. died before reaching twenty-eight days of age. The neonatal mortality rate for premature infants who weighed 1000 gm. or less at birth was almost twenty times higher than the rate for those who weighed more than 2000 gm. Only 8 per cent of all the premature infants weighed 1000 gm. or less at birth, yet almost 40 per cent of the deaths occurred in this group.

There were 67 premature infants reported to us who were not weighed at birth; of these, 52 died. Since we did not have any data on length of gestation, we did not estimate birth weight in these cases but kept them as a separate group. Probably most of these 67 were in low-weight groups. The weight may not have been recorded because the attending physicians considered the infants so puny that they should not be subjected to the trauma of weighing.

Female premature infants showed a definite superiority to male premature infants in ability to survive. Only 16 per cent of the females as compared to 24 per cent of the males died during the first twenty-eight days of life (Table 5). This superiority of the female holds true for all weight groups, being greatest for the heavier and least for the very small infants; the neonatal mortality for males weighing 1000 gm. or less at birth is only 2 per cent higher than that for females.

TABLE 5. *Neonatal Mortality Rates among Premature Births by Birth Weight, Sex and Plurality of Birth (Massachusetts, 1951).*

Sex and Plurality of Birth	Neonatal Mortality Rates by Birth Weight				
	All weight groups	Infants weighing 1000 gm. or less	Infants weighing 1001–1500 gm.	Infants weighing 1501–2000 gm.	Infants weighing 2001–2500 gm.
	%	%	%	%	%
All premature infants	20.1	93.8	57.8	18.4	4.7
Male	24.3	94.6	65.8	21.8	6.9
Female	16.4	92.9	49.6	15.3	2.9
Single births	20.1	94.6	57.9	20.6	5.0
Male	24.1	95.3	66.5	24.0	7.3
Female	16.6	93.9	49.7	17.3	3.1
Plural births	20.2	90.8	57.6	10.9	3.2
Male	25.1	92.5	63.6	13.5	4.5
Female	15.5	88.2	48.6	8.8	2.0

TABLE 6. *Neonatal Mortality Rates among Premature Infants Born in Maternity Hospitals by Birth Weight and Hospital Size (Massachusetts, 1951).*

Hospital Size*	Neonatal Mortality Rates by Birth Weight				
	All premature infants	Infants weighing 1000 gm. or less	Infants weighing 1001–1500 gm.	Infants weighing 1501–2000 gm.	Infants weighing 2001–2500 gm.
	%	%	%	%	%
All maternity hospitals	19.5	93.9	57.3	17.8	4.6
Hospitals with 1000 or more births	18.7	92.0	53.8	16.8	4.2
Hospitals with 500–999 births	20.1	95.5	58.7	20.2	4.6
Hospitals with less than 500 births	21.2	97.6	70.6	15.8	6.5

*Grouped according to the number of live births in 1951.

Plural-born premature infants have a better chance of survival than single-born premature infants. The neonatal mortality rates are lower in all weight groups for plural than for single births. The rates for the totals in both groups are about the same because there was a much higher proportion of infants in the low-weight groups among the plural than among the single births (Table 3). This superiority of plural-born infants over single-born infants holds for both male and female premature infants.

There were 213 nonwhite premature births reported to the Department; 36 deaths occurred among these infants. Seventeen per cent of these infants died in the neonatal period compared with 20 per cent of the white premature infants. In all but one weight group the mortality rate for nonwhite was lower than that for white premature infants. The differences were not statistically significant. Since there were so few nonwhite premature infants, no further breakdown was made by race.

Neonatal Mortality among Premature Infants by Hospital Size

In 1951, 5348 premature births were reported to the Department; 5211 of these infants were born in maternity hospitals. There were 1016 neonatal deaths among those born in maternity hospitals. These deaths have been considered according to the place of birth regardless of the place of death. In Table 6 the variation in the neonatal mortality rates are shown by hospital size. The rates among premature infants were inversely related to the size of hospital. The smaller hospitals had the higher rates in all but one birth weight group (1501 to 2000 gm.). These differences may have been due to the variation in the completeness of reporting of premature births.

Of the total 5348 premature infants reported only 217 (4 per cent) were transferred from one hospital to another or from home to hospital. Generally, the smaller infants were transferred to other hospitals. It is therefore not surprising that 41 per

Table 7. *Neonatal Deaths among Premature Infants by Birth Weight and Age (Massachusetts, 1951).*

Age at Death	Deaths in All Weight Groups	Deaths Among Infants Weighing 1000 Gm. or Less	Deaths Among Infants Weighing 1001–1500 Gm.	Deaths Among Infants Weighing 1501–2000 Gm.	Deaths Among Infants Weighing 2001–2500 Gm.	Deaths Among Infants with Weight Not Reported
Under 1 hr.	113 (10%)	59 (15%)	22 (8%)	11 (5%)	10 (6%)	11 (21%)
1–23 hr.	502 (47%)	234 (59%)	118 (44%)	71 (35%)	51 (33%)	28 (54%)
1–6 days	402 (37%)	96 (24%)	111 (41%)	106 (51%)	76 (49%)	13 (25%)
7–27 days	60 (6%)	6 (2%)	18 (7%)	18 (9%)	18 (12%)	— —
Totals	1077 (100%)	395 (100%)	269 (100%)	206 (100%)	155 (100%)	52 (100%)

Table 8. *Neonatal Deaths among Premature Infants according to Main Causes by Birth Weight and Age (Massachusetts, 1951).*

Cause of Death	List Number*	Total Neonatal Deaths	Infants Weighing under 1000 Gm. no. of deaths	Infants Weighing 1001–1500 Gm. no. of deaths	Infants Weighing 1501–2000 Gm. no. of deaths	Infants Weighing 2001–2500 Gm. no. of deaths	Weight Not Stated no. of deaths	Infants Under 1 Day Old no. of deaths	Infants 1–6 Days Old no. of deaths	Infants 7–27 Days Old no. of deaths
All causes		1053†	383	263	202	153	52	594	399	60
Certain diseases of early infancy	760–76	999	380	254	187	127	51	570	379	50
With immaturity		943	377	245	177	93	51	545	352	46
Without immaturity		56	3	9	10	34	—	25	27	4
Immaturity unqualified	776	570	308	124	75	29	34	382	167	21
Postnatal asphyxia and atelectasis	762	304	44	96	84	69	11	132	158	14
With immaturity		277	44	93	78	51	11	117	146	14
Without immaturity		27	—	3	6	18	—	15	12	—
Birth injuries	760–1	78	21	22	13	17	5	42	31	5
With immaturity		59	18	18	11	7	5	34	22	3
Without immaturity		19	3	4	2	10	—	8	9	2
Pneumonia of newborn	763	18	2	3	7	6	—	1	7	10
With immaturity		14	2	2	7	3	—	1	5	8
Without immaturity		4	—	1	—	3	—	—	2	2
Hemolytic diseases of newborn	770	10	—	3	3	4	—	7	3	—
With immaturity		7	—	2	2	3	—	5	2	—
Without immaturity		3	—	1	1	1	—	2	1	—
Other diseases of early infancy	764–9, 771–4	19	5	6	5	2	1	6	13	—
With immaturity		16	5	6	4	—	1	6	10	—
Without immaturity		3	—	—	1	2	—	—	3	—
Congenital malformations	750–9	49	3	9	13	23	1	22	18	9
All other conditions	Residual	5	—	—	2	3	—	2	2	1

**International List* numbers, sixth revision.

†There were 1077 deaths; 24 deaths were omitted because 10 were reported as stillbirths on the death certificates and in 14 no death certificates were found.

cent of those who were transferred to another hospital died during the neonatal period, as compared with 19 per cent for those who were not transferred.

Neonatal Deaths among Premature Infants by Age

More deaths in the neonatal period occurred during the first day of life than in the remaining twenty-seven days combined (Table 7); 57 per cent of the infants died during the first twenty-four hours of life. This proportion varied inversely with birth weight. Seventy-four per cent of the infants weighing 1000 gm. or less at birth, 52 per cent weighing 1001 to 1500 gm., and 40 per cent weighing over 1500 gm. died during the first day of life. The risk of dying decreased with increasing age. Only 6 per cent of the total neonatal deaths occurred after the first week of life.

Table 9. *Distribution of Neonatal Deaths among Premature Infants according to Main Causes by Birth Weight and Age (Massachusetts, 1951).*

Cause of Death	International List Number	All Neonatal Deaths	Neonatal Deaths among Infants Weighing under 1000 Gm.	Neonatal Deaths among Infants Weighing 1000-1500 Gm.	Neonatal Deaths among Infants Weighing 1501-2000 Gm.	Neonatal Deaths among Infants Weighing 2001-2500 Gm.	Neonatal Deaths among Infants with Weight Not Stated	Neonatal Deaths among Infants under 1 Day Old	Neonatal Deaths among Infants 1-6 Days Old	Neonatal Deaths among Infants 7-27 Days Old
		%	%	%	%	%	%	%	%	%
All causes		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Certain diseases of early infancy	760-76	94.9	99.2	96.6	92.6	83.0	98.1	96.0	95.0	83.3
With immaturity		89.6	98.4	93.2	87.6	60.8	98.1	91.8	88.2	76.7
Without immaturity		5.3	0.8	3.4	5.0	22.2	—	4.2	6.8	6.6
Immaturity unqualified	776	54.1	80.4	47.1	37.1	19.0	65.4	64.3	41.9	35.0
Postnatal asphyxia and atelectasis	762	28.9	11.5	36.5	41.6	45.1	21.2	22.2	39.6	23.3
With immaturity		26.3	11.5	35.4	38.6	33.3	21.2	19.7	36.6	23.3
Without immaturity		2.6	—	1.1	3.0	11.8	—	2.5	3.0	—
Birth injuries	760-1	7.4	5.5	8.4	6.4	11.1	9.6	7.1	7.8	8.3
With immaturity		5.6	4.7	6.8	5.4	4.6	9.6	5.7	5.5	5.0
Without immaturity		1.8	0.8	1.5	1.0	6.5	—	1.3	2.3	3.3
Pneumonia of newborn	763	1.7	0.5	1.1	3.5	3.9	—	0.2	1.8	16.7
With immaturity		1.3	0.5	0.8	3.5	2.0	—	0.2	1.3	13.3
Without immaturity		0.4	—	0.4	—	2.0	—	—	0.5	3.3
Hemolytic diseases of newborn	770	0.9	—	1.1	1.5	2.6	—	1.2	0.8	—
With immaturity		0.7	—	0.8	1.0	2.0	—	0.8	0.5	—
Without immaturity		0.3	—	0.4	0.5	0.7	—	0.3	0.3	—
Other diseases of early infancy	764-9, 771-4	1.8	1.3	2.3	2.5	1.3	1.9	1.0	3.3	—
With immaturity		1.5	1.3	2.3	2.0	—	1.9	1.0	2.5	—
Without immaturity		0.3	—	—	0.5	1.3	—	—	0.8	—
Congenital malformations	750-9	4.6	0.8	3.4	6.4	15.0	1.9	3.7	4.5	15.0
All other conditions	Residual	0.5	—	—	1.0	2.0	—	0.3	0.5	1.7

Neonatal Deaths by Cause

The distribution of neonatal deaths by main causes is given in Table 8. Twenty-four neonatal deaths were omitted. No death certificates were found for 14 of these. The other 10 were reported as stillbirths on the death certificates. Massachusetts has no special certificate for reporting stillbirths, which are reported on both birth and death certificates. The birth certificates reported these 10 births as live births, and the death certificates reported them as stillbirths. The Division of Vital Statistics of the Office of the Secretary of the Commonwealth has queried the physicians attending these cases to make the necessary corrections.

Ninety per cent of the neonatal deaths were assigned to certain diseases of infancy with mention of immaturity, 5 per cent to certain diseases of early infancy without mention of immaturity, and almost all the remaining 5 per cent to congenital malformations (Table 9). There was little variation in these percentages between male and female infants and between single and plural births.

The percentage distribution of the neonatal deaths for main causes among the smaller premature infants was quite different from that for the larger ones. Ninety-eight per cent of the neonatal deaths among infants weighing 1000 gm. or less at birth were assigned to certain diseases of early infancy with mention of immaturity. Only 61 per cent among those weighing more than 2000 gm. at birth were assigned to this classification.

Fifty-four per cent of the total neonatal deaths were assigned to immaturity unqualified, 29 per cent to postnatal asphyxia and atelectasis, 7 per cent to birth injuries and 10 per cent to all other causes. This order of rank held for premature infants weighing 1500 gm. or less at birth; however, for those weighing more than 1500 gm., postnatal asphyxia and atelectasis was the leading cause, followed by immaturity unqualified and congenital malformations.

The leading causes of death during the first week of life were also immaturity unqualified, postnatal asphyxia and atelectasis and birth injuries, accounting for 92 per cent of the deaths during this period. After the first week of life, birth injuries dropped from third to fifth place as a leading cause of death, being outranked by pneumonia of the newborn and congenital malformations.

Discussion

The study of the epidemiology of premature birth in Massachusetts and the evaluation of programs aimed at reducing the consequent mortality are seriously handicapped by the lack of complete factual data concerning incidence. In all other states the incidence can be determined from an analysis of the birth certificates. However, the fact that Massachusetts is the only state in which birth weight is not recorded on the birth certificate prevents that document from being used for this purpose. The reporting of premature births as required by law is only 80 per cent complete. Completeness of reporting varies with hospital size, the smaller institutions submitting less complete reports.

The Act of 1949, in our opinion, has been successful in its purpose of providing hospital care to infants weighing 4½ pounds or less at birth whose parents are unable to pay for such care. This act has helped to deter parents from taking their infants out of hospitals before doctors considered the child robust enough to go home. It has also helped the individual hospitals to meet some of the deficits that they formerly acquired by giving care to such infants. The hospital care of the premature infant can be extremely expensive; cases in which a hospital stay of three months or more is required are not infrequent.

Another and unexpected result of the Act of 1949 has been its educational value. As a result of this law, it is believed that every hospital administrator, every member of local boards of health and the great majority of selectmen now recognize that premature birth is a serious health problem. They have been led to this conclusion by a consideration of the cost of hospital care of these infants and the methods of appropriating money to pay for it.

Summary

Birth weight is not reported on birth certificates in Massachusetts. To define the problem of premature birth and to plan and evaluate programs in this state, information on premature births must be obtained from other sources. The two sources from which data can be obtained are described.

Six and seven-tenths per cent of the infants born alive in Massachusetts weighed 5½ pounds or less at birth. One out of every 5 premature infants born in the Commonwealth did not survive the first month of life. These statistics compare favorably with those from other states. From the data presented in this paper it appears that mortality rates are higher in the small hospitals. It would be of interest to know whether this would hold true if reporting of premature births were more complete. It is hoped that this paper will demonstrate to physicians that complete reporting is necessary if the size of the problem in Massachusetts is to be determined, and it is hoped that the district medical societies and other medical groups will take an interest in this matter and make a special effort to obtain more complete reporting by hospitals.

OBSERVATION ON THE PATHOGENESIS OF LARYNGEAL GRANULOMA DUE TO ENDOTRACHEAL ANESTHESIA

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THE first case of laryngeal granuloma due to endotracheal anesthesia was described in 1932 by Clausen.[1] Since then about 50 cases have been reported in the literature, and undoubtedly many additional ones are unreported. It is the purpose of this paper to report an original observation on the causative factors of this relatively rare complication, and to describe the growth of the lesion in the hope that certain preventive measures will be followed in the future.

Materials and Methods

This study is based on 4 cases of laryngeal granuloma due to endotracheal anesthesia and, in addition, presents a clinical analysis of the location of endotracheal tubes in the glottis.

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Case Reports

Case 1. A 38-year-old man had been hoarse ever since a spinal fusion under endotracheal anesthesia had been performed for rheumatoid arthritis in 1949. He had the typical feeling of "something in the throat" and an occasional sharp, stabbing pain in the larynx with a choking sensation. Examination revealed a 5-mm. pedunculated mass arising from the vocal process of the left arytenoid cartilage. Because of the absolute rigidity of the spine, direct laryngoscopy was impossible, and the lesion was excised by thyrotomy. Healing was uneventful, and there has been no recurrence.

Case 2. A 55-year-old woman had undergone a removal of a herniated nucleus pulposus and spinal fusion. Two days after operation fever, hoarseness and a sore throat developed. Throat culture revealed a hemolytic streptococcus, resistant to penicillin but sensitive to terramycin. The report did not come back from the laboratory for 6 days, during which the patient was on 600,000 units of penicillin intramuscularly and was not improving. When penicillin was discontinued and terramycin started, she recovered rapidly except for the loss of voice. One month later she consulted me complaining of hoarseness and was seen to have a pedunculated mass, 2 by 3 mm., arising from the vocal process of the right arytenoid cartilage.

This lesion healed spontaneously over a period of 3 months on terramycin and rest for the voice and body.

Case 3. A 44-year-old woman had been hoarse ever since a craniotomy performed 6 months previously under endotracheal anesthesia. A large (1 cm. in diameter) pedunculated polyp was seen to be attached to the right vocal process. This was removed by suspension laryngoscopy. Recovery was uneventful and complete.

Case 4. An 88-year-old woman had a tracheal neoplasm. A thyrotomy was performed, and the thyroid gland, cricoid cartilage and the upper 5 tracheal rings were incised in the midline. This procedure was performed under local anesthesia, with the bronchoscope in the trachea, and afforded an opportunity to visualize the location of the rigid bronchoscope in the glottis in an anterior position and without pressure on the arytenoid cartilage, vocal processes or posterior commissure (Fig. 1 and 2).

FIGURE 1. *Diagram Indicating the Position of the Rigid Bronchoscope in the Glottis in Sagittal Section (Note Its Location Anteriorly).*

Because the local anesthesia was incomplete, it was decided to pass an endotracheal tube through the mouth and into the trachea to effect general anesthesia with a closed system. The intubation was done with ease, after the vocal cords had been seen to be normal. A marked difference in location of the flexible rubber endotracheal tube was immediately apparent under general anesthesia. The arytenoid cartilages were parted wide, and the tube lay directly between the vocal processes (Fig. 3 and 4). With each swallow, cough and manipulation of the trachea, there was an obvious friction on the epithelium of the true cords overlying the vocal processes. These could be seen to pinch the tube like pincers when the patient swallowed or coughed.

FIGURE 2. *Diagram Showing the Bronchoscope in the Glottic Chink as Visualized from above.*
The tube can be seen against the anterior commissure remote from the vocal processes.

When the tube was removed a denuded area, 3 mm. in diameter, could be seen on the right vocal process with bare cartilage protruding. This could also be seen 3 days after operation by mirror, with considerable edema and ecchymosis surrounding it. As the swelling subsided a sessile mass of granulation tissue appeared on the right vocal process in the same exposed area and in 3 weeks became polypoid, with a definite stalk. This was later excised through a laryngoscope, and the patient recovered uneventfully. It was, therefore, my privilege to observe the pathogenesis from beginning to end most dramatically.

FIGURE 3. *Diagram Indicating the Position of the Flexible Endotracheal Tube in the Glottis in Sagittal Section (Note Its Location Posteriorly).*

The important observation in this case is one that has apparently never before been reported, and that is the marked difference in anatomic position in the glottis between a rigid bronchoscope under local anesthesia and a flexible endotracheal tube under general anesthesia. There is a significantly different position in the glottic chink and in the hypopharynx as well.

FIGURE 4. *Diagram Showing the Endotracheal Tube in the Glottic Chink as Visualized from above.*
The tube can be seen against the posterior commissure pinched by the vocal processes.

ETIOLOGY

The causes of laryngeal granuloma due to endotracheal anesthesia may be divided into three classes: endolaryngeal trauma, extralaryngeal trauma and infection. One of the less common endolaryngeal factors is a traumatic intubation in which the tube is forced between the adducted cords, usually posteriorly. Another is a prolonged anesthesia with the endotracheal tube in place. This time factor and the occasional use of too large a tube are less common etiologic elements. On the other hand, head position is most important as a cause of endolaryngeal trauma, as evidenced by

the fact that all my cases and nearly 40 per cent of those reported in the literature were back or head operations with the patient in a head-down position. This, I believe, is a major cause of laryngeal granuloma because it forces the tube into the posterior commissure and against the vocal processes. All the lesions reported to date have occurred in this area.[2]

Trauma to the vocal processes almost never happens with bronchoscopy because of the difference in the position of the tube in the glottis—the bronchoscope resting anteriorly away from the vocal processes, whereas the endotracheal tube is held directly between them.

The role of extralaryngeal trauma is somewhat different. The tube may be imagined as pinched between the arytenoid cartilages, with the trachea and larynx moving up and down or pulling laterally on the tube. This commonly occurs in a thyroidectomy or in too light an anesthesia with the resultant swallowing and coughing. The vocal processes scrape and slide on the tube with considerable friction. It is important not to manipulate the larynx and trachea during neck operations while the tube is in place. Statistically, another 40 per cent of the reported cases of laryngeal granuloma occur in thyroidectomy operations. This, then, is a major cause.

The role of infection is often overlooked. Many of the patients described in the literature suffered febrile upper respiratory infections immediately before operation, and I believe this to be an important etiologic element. In 1 of the cases reported above (Case 2) a hemolytic streptococcus was cultured from the pharynx, and the appearance at the laryngeal inflammation suggested infection rather than trauma.

Pathogenesis

In Case 4 it was possible to visualize directly the pathogenesis of laryngeal granuloma step by step. These may be outlined as follows:

In the first place, trauma causes an abrasion on the vocal process that exposes cartilage and results in a perichondritis. The actual abrasion may be microscopic in size.[3]

Secondly, the abrasion becomes a so-called contact ulcer because of secondary infection.

Thirdly, the contact ulcer becomes a sessile granuloma as the denuded area is covered with granulations in an attempt to cover the bare cartilage and heal.

Fourthly, the granuloma becomes an inflammatory polyp by the proliferation of the central tissue and the healing or epithelization of the periphery. This changes a sessile mass into a pedunculated polyp of pyogenic granuloma.

Finally, healing or epithelization of these lesions is the last and sometimes the most difficult stage. Voice rest is, of course, essential; otherwise, the constant trauma resulting when the vocal processes adduct and collide in the midline will lead to the most obstinate "kissing ulcers" and bilateral granulomas. Recurrences after laryngoscopic removal are not uncommon because of this vocal abuse.

Discussion

This type of trauma is primarily to the glottis, but there is considerable injury to the subglottic trachea at times. When this occurs, it has been reported on the posterior tracheal wall in conformity with the theory postulated above.[4] Surgical removal is most likely to be successful when the lesion has reached the fourth stage and has a clearly defined pedicle. An attempt at excision during the third—or sessile—stage should be avoided. Cases have been reported in which the healing of the ulcer from its periphery eventually constricted the polypoid mass off at its base and the patient coughed up the entire polyp—a self-amputation. This, however, is not recommended as treatment, since many patients have serious dyspnea with the laryngeal obstruction and need emergency surgery.

Summary and Conclusions

A complete understanding of the etiology and pathogenesis of laryngeal granuloma due to endotracheal anesthesia will aid greatly in the prevention and care of this lesion. Some of the prophylactic measures suggested by this study are as follows: one should avoid a sharply flexed head position and strive for a hyperextension, as in direct laryngoscopy; one should avoid forcing a tube through a laryngeal spasm; one should avoid the use of a large tube to prevent aspiration, substituting a smaller one with an inflated cuff; one should avoid extralaryngeal trauma during neck operations; and one should avoid infection by the use of a sterile technic for intubation and antibiotics postoperatively.

The observation of the significantly different glottic positions of an endotracheal tube under general anesthesia and a bronchoscope under local anesthesia makes it easier to understand the greater incidence of laryngeal granuloma and other traumatic lesions in endotracheal anesthesia than in bronchoscopy. The pathogenesis of laryngeal granuloma is described.

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References

1. Clausen, R. J. Unusual sequela of tracheal intubation. *Proc. Roy. Soc. Med.* **25**:1507, 1932.
2. Hill, F. T. Granuloma of larynx following endotracheal anesthesia. *Ann. Otol. Rhin. & Laryng.* **59**:910-913, 1948.
3. Baron, S. H., and Kohlmoos, H. W. Laryngeal sequelae of endotracheal anesthesia. *Ann. Otol. Rhin. & Laryng.* **60**:767-792, 1951.
4. Etsten, B., and Mahler, S. Sub-glottic membrane: complication of endotracheal intubation. *New Eng. J. Med.* **245**:957-960, 1951.

MEDICAL PROGRESS

HOMEOSTATIC LIMITS TO SAFE PARENTERAL FLUID THERAPY*

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A LEGEND displayed over the old apothecary shop in Williamsburg, Virginia, reads, "Deus major agit." When Walter Cannon entitled his book on homeostatic reactions *The Wisdom of the Body* he re-emphasized the role of innate forces in healing. The present report explores the possibility of so designing parenteral fluid therapy that patients may make full use of their homeostatic mechanisms during the critical period when the physician's order, rather than instinct, prescribes water and solute intake.

The following sections deal, respectively, with the homeostatic mechanisms pertinent to the water, sodium, potassium, phosphate and dextrose needs of patients whose illness prescribes intravenous infusion therapy. An attempt is made to indicate in approximate terms both the least amount of each substance needed to correct or prevent abnormal body deficits and the greatest amount that can be administered without upsetting concentrations or volumes of body fluids to a pathologic degree. The manner in which the organism can retain or reject intermediate amounts in accordance with its best interests is then discussed and exemplified. All results are expressed on a basis of square meter of body surface, since this makes them applicable to patients of all ages.[1]

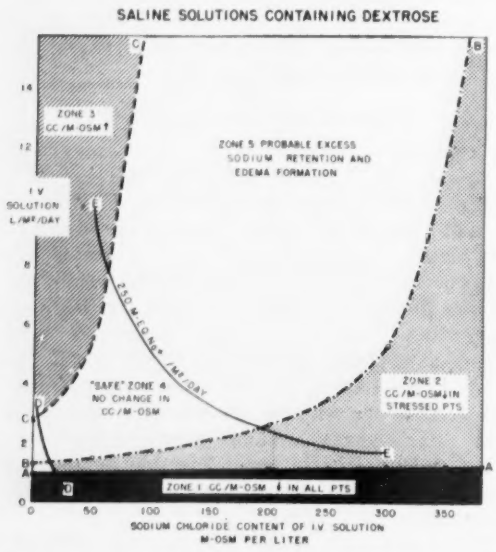
SALINE SOLUTIONS CONTAINING DEXTROSE
ZONE 3 GC/M-OSM↑
ZONE 5 PROBABLE EXCESS SODIUM RETENTION AND EDEMA FORMATION
I.V. SOLUTION L/M²/DAY
250 M-EQ Na⁺ / M²/DAY
"SAFE" ZONE 4 NO CHANGE IN GC/M-OSM
ZONE 2 GC/M-OSM↓IN STRESSED PTS
ZONE 1 GC/M-OSM ↓ IN ALL PTS
SODIUM CHLORIDE CONTENT OF I.V. SOLUTION M-OSM PER LITER

FIGURE 1. *Minimum Requirement and Maximum Tolerance for Saline-Dextrose Solutions of Various Strengths (See Text for Descriptive Comments).*

MINIMUM REQUIREMENTS AND LIMITS OF WATER TOLERANCE

Figure 1 is concerned with the effect on body-water concentration of infusing solutions that contain, in addition to dextrose, sodium chloride in concentrations from 0 to 350 m-osm. (milliosmols)¶ per liter. The left-hand ordinate of this figure indicates the rate of fluid infusion expressed in liters per square meter per twenty-four hours. The scale along the abscissa indicates the sodium chloride content of the fluid infused expressed as milliosmols per liter. The theoretical effects of the administration of various amounts of fluids of varying salt content upon the recipient's body-water concentrations expressed as cubic centimeters per m-osm. of total solute are suggested by the zones defined by curves A to E, each of which is discussed in detail below.

Before a description of the manner in which these curves have been derived is undertaken it may be well to outline the reasons for making a distinction between dextrose and the inorganic solutes of parenteral fluids. When in solution a mol of dextrose has essentially the same osmotic properties as a mol of sodium, potassium, chloride or phosphate. After entering the body, however, dextrose is usually oxidized to carbon dioxide and water or converted to osmotically inactive glycogen or fat so rapidly that it exerts only a small effect on the osmolar concentration of body fluids. Also, in the absence of abnormal hyperglycemia, dextrose is not excreted in the urine. By contrast, sodium, chloride and other inorganic solutes of infusion fluids are osmotically active substances during their stay in the body and during excretion in the urine. Thus the inorganic solutes contained in parenteral fluids are important determinants of water-solute relations in body fluids and urine.

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¶In the case of univalent electrolytes like sodium, potassium and chloride ion, 1 milliequivalent is equal to 1 m-osm. Thus isotonic saline solution contains approximately 150 m-osm. of sodium and 150 m-osm of chloride or a total of 300 m-osm of inorganic solute per liter.

Minimum Water Requirement of a Person Not under Stress (Curve A, Fig. 1)

The minimum water requirement of a person receiving only parenteral fluids is equal to the sum of his minimum renal and extrarenal water losses minus water of oxidation of glucose infused and body substance catabolized and the water content of the catabolized body substance. Insensible water loss of sick patients has been estimated as 1000 cc. per square meter per day. This approximates the average value obtained on a group of 40 hospitalized infants, children and adolescents whose insensible water losses were measured over twenty-four-hour periods of ordinary hospitalization.[2] This figure is roughly 70 per cent greater than values obtained by others on strictly basal, older subjects.[3,4] Gastrointestinal losses are assumed to be zero, since they are usually negligible in persons receiving only fluids by the parenteral route. Water of oxidation plus water content of body substance catabolized has been taken as 270 cc. per square meter per day.[3,5,6]* Minimum urine water is considered to be a function of two variables—namely, urine water concentration and urine solute output.[1,7]

Minimum urine water concentration (α) has been taken as 0.7 cc. per milliosmol.[7,8] Endogenous urine solute excretion has been estimated as 200 m-osm. per square meter per day for persons who are given enough water to meet water needs and enough dextrose to eliminate ketosis and to minimize nitrogen catabolism. The smallest quantity of dextrose that will permit such a reduction of solutes in the urine is 50 to 75 gm. per square meter per day.[5,6] It is assumed that the infusions indicated in Figure 1 are made up to provide this but not an excessive amount of dextrose.

Although a portion of the exogenous solutes administered intravenously may be retained for repair of deficits during early phases of parenteral fluid therapy, maintenance of normal body concentrations and volumes depends upon their quantitative excretion in the urine as soon as repair and abnormal maintenance needs have been met. Figure 1, therefore, is constructed on the assumption that the total urinary solute output is equal to the sum of the aforementioned endogenous (S_E) plus the exogenous inorganic solutes contained in the fluid infused (S_I).† Minimum urine volume, then, is equal to total solute output, $S_E + S_I$ times the minimum value for urine water concentration (cc. of water per milliosmol) observed under conditions of need for water conservation.

It is evident from the foregoing that the quantity of fluid needed to cover minimum body-water expenditures (Curve A, Fig. 1) is determined not only by such essential factors as insensible water loss and the water required for the renal excretion of the minimal endogenous solute output, but also by the inorganic solute content of the fluid

TABLE 1. *Effects of Administering Too Little or Too Much Water and Certain Solutes.*

		Amount Administered		
		Too Little		Too Much
Water	A.	Hemoconcentration Thirst Oliguria Fever Circulatory failure[1, 9, 10]	B.	Hemodilution Polyuria Intracranial hypertension Headache Weakness Muscle twitchings Convulsions Coma Death[1, 11-13]
Sodium	C.	Extracellular fluid volume decreased Loss tissue elasticity Microcardia Hypotension Circulatory failure[1, 9, 10]	D.	Extracellular fluid volume increased Edema formation Tendency to potassium deficiency (See section E)[14-17]
Potassium	E.	Apathy Lethargy Muscle weakness Electrocardiographic changes Ileus or diarrhea Hypopotassemia Metabolic alkalosis[18-20]	F.	Hyperpotassemia Electrocardiographic changes Muscle weakness Cardiac arrest[19, 21]
Phosphorus	G.	Hypophosphatemia ? Other effects[1, 22, 23, 24]	H.	Hyperphosphatemia Hypocalcemia Tetany Death[1]
Carbohydrate	I.	Ketosis Protoplasmic catabolism Tendency to greater water and electrolyte losses[3, 6]	J.	Hyperglycemia Glycosuria Hepatic failure Death[25]

*Patients receiving adequate amounts of dextrose catabolize body protoplasm at a rate of approximately 120 gm. per square meter per day. Of this protoplasm about 60 per cent, or 70 cc., is water.

†One may find the value for S_I at any position within Figure 1 by multiplying the value for fluid volume shown by the ordinate scale by the corresponding inorganic solute concentration value indicated by the abscissa scale.

being infused.* In this connection Curve A indicates that the minimum water requirement is less when one infuses a solution of dextrose without inorganic solutes than when one infuses such a solution as dextrose in isotonic saline solution, which contains 300 m-osm. of inorganic solute per liter.

Failure to meet the minimum water requirement described by Curve A-A places the patient in the underlying Zone 1 of Figure 1. Under this circumstance he is obliged to supply the difference between water intake and minimum water requirement by expending a portion of his body-water stores. A tendency to decreased body-water concentration results (that is, cc. of water per m-osm. of solute falls). As outlined in Section A of Table 1, the earliest signs of decreased body-water concentration are thirst and a tendency to oliguria. As reduction in body-water concentration progresses, hemoconcentration, fever and circulatory failure may become manifest.[1,9,10]

Minimum Water Requirement of Patients under Stress (Curve B, Fig. 1)

Patients under severe stress as a result of acute illnesses frequently lose their capacity to excrete the highly concentrated urine (0.7 cc. per milliosmol) that can be formed by persons not under stress. Instead, even in the presence of dehydration, they may pass urine having a water concentration as high as 2.5 cc. per milliosmol. of solute.[25-27] This value was used as the minimum urine water concentration of such patients in the construction of Curve B of Figure 1.

Comparison of Curves B and A shows that the amounts of infusion fluid of varying solute content necessary to balance the minimum water expenditures of patients under stress may be considerably greater than those of persons not under stress. Curve B calls attention to the striking possibility that as much as 5 liters per square meter per day of a solution as rich in solutes as isotonic saline (300 m-osm. of inorganic solutes per liter) may be needed to provide the minimum water requirement of a severely stressed patient. However, as pointed out below, the infusion of such a volume of isotonic saline solution would involve the administration of a quantity of sodium ion (750 milliequiv. or 43 gm. of sodium chloride per square meter per day) that overtaxes the capacity of the mechanisms responsible for body sodium homeostasis.

Failure to meet the minimal fluid needs of patients under stress results in the changes listed in Section A of Table 1.

Maximum Water Tolerance (Curve C, Fig. 1)

The means employed above for estimating minimum water requirement can also be used to estimate the largest quantity of various types of solution that the organism can tolerate. The two principal variables concerned with maximum water tolerance are the ability of the kidney to dilute urine and the maximum renal excretory capacity for water. Under conditions of excess water intake, the kidneys form urine containing up to approximately 10 cc. of water per milliosmol of solute.[1,28] Curve C-C is constructed with this value for urine water concentration. The intersect of Curve C with the left-hand ordinate at about 2700 cc. per square meter per day (115 cc. per square meter per hour or 30 drops per square meter per minute) describes the low body tolerance for simple dextrose in water solutions, even when there are no abnormal limitations to dilution of urine such as may occur with anesthesia and morphine therapy. As evidenced by the sharp upward slope of this curve, fluid tolerance is increased markedly by the addition of as little as 50 to 80 m-osm. of inorganic solutes to each liter of dextrose solution.

Since the kidneys are unable to form urine at a rate in excess of about 15 liters per square meter per twenty-four hours[1,29] there is a ceiling value for water intake of approximately 15.7 liters per square meter per day (15 liters of urine plus 1 liter of insensible water minus 0.3 liter of water of oxidation and content of tissue catabolized). This explains why Curve C-C of Figure 1 abruptly becomes horizontal when it reaches this value (Segment C-B).

Administration of water in excess of tolerance results in an increase in cubic centimeters of body water per milliosmol of solutes (Zone 3, Fig. 1). When body-water concentration becomes pathologically increased, signs of water intoxication develop (Section B of Table 1). In the initial phases of this condition, patients pass dilute urine of generous volume. Terminally, however, oliguria and even anuria may develop.[1] The cause of such an untoward course of events may be missed, for autopsy examination of laboratory animals that die as a result of water intoxication often fails to reveal any changes other than slight congestion of the liver and kidneys. Anasarca formation and localized edema are notably absent.[12]

The foregoing indicates that the infusion of fluid of salt concentrations and at rates that lie within the area bounded by Curves B-B and C-C (Zones 4 and 5) is compatible with body-water or body-

*The following formula, for which we are indebted to Dr. Daniel Clement, is included for the convenience of readers who wish to reconstruct curves A, B and C of Figure 1 (they may reproduce Curve A with the aid of this equation by inserting the values for I. W., W. Ox plus W. T. and S_g mentioned in the preceding paragraphs, by assuming values for C ranging between 0 and 0.35 and by solving for V):

$$V = \frac{[(I.W. - W.Ox. - W.T.) + (S_g a)]\ \frac{1}{a}}{\frac{1}{a} - C}$$

Where V = volume of fluid infused (cc/m²/day),
I.W. = insensible water loss (cc/m²/day),
W.Ox. = water of oxidation (cc/m²/day),
W.T. = water content of tissue catabolized,
S_g = endogenous urine solutes (m-osm/m²/day),
a = urine water concentration (cc/m-osm) and
C = inorganic solute concentration of V (m-osm/cc).

solute concentration homeostasis. However, as discussed in the following section, such infusions may not be compatible with volume or body-solute content homeostasis.

Limits of Tolerance for Certain Solutes

In addition to body-water concentration homeostasis, body-water volume homeostasis is an important consideration in parenteral fluid therapy. Under normal conditions where body-water concentration — that is, cubic centimeters of body water per milliosmol of solute — is kept constant by the neurohypophyseal-renal homeostatic system, body-water volume is a variable dependent upon body-solute content. As illustrated with respect to sodium, potassium and inorganic phosphorus in the sections that follow, homeostatic function normally attempts to keep the body's content of each constituent of body solute at its physiologically optimal amount.

Sodium Homeostasis

Most normal persons take and excrete, largely by way of the kidneys, between 50 and 70 milliequiv. of sodium per square meter per day.[30] Sudden reduction of the sodium intake to very low levels is followed by a gradual compensatory decrease in urinary sodium output. Ordinarily, three to five days are needed for the adrenocortical-renal homeostatic mechanism to complete this adjustment.[22,31,32] During the interval, the patient is in negative sodium balance. Usually this negative balance does not amount to more than about 2 milliequiv. per kilogram of body weight, a quantity equal to approximately 5 per cent of adult body sodium stores.[33,34] Since approximately 25 per cent of body sodium stores must be lost before the gross symptoms and signs of sodium deficiency develop (Section C of Table 1), sudden sodium deprivation is well tolerated by the normal person.[1,9,10]

Under conditions of complete sodium deprivation, healthy persons can reduce their rate of sodium excretion by all routes to levels of approximately 10 milliequiv. per square meter per day.[5, 21, 23] It follows that this is the smallest sodium intake that may be considered compatible with sodium balance. This is diagrammatically represented by Curve D-D of Figure 1.

An abrupt increase in sodium intake leads to a positive sodium balance. Increased body sodium content normally is followed by decreased production of the adrenocortical hormones having sodium-retentive properties.[35] Urinary sodium output then tends to rise until body sodium homeostasis becomes re-established. This homeostatic response may require three to five days for completion.

Provided sufficient time is allowed for such adaptive changes to occur, normal persons can achieve sodium balance on intakes of as much as 700 milliequiv. per square meter per day.[36] However, such large quantities of sodium should not be considered physiologically tolerable for patients undergoing parenteral fluid therapy, for during the period of adaptive response there may be accumulation of excessive amounts of sodium with formation of edema fluid. Retentions amounting to about 4 milliequiv. per kilogram of body weight have been observed after sudden increase of 50 to 120 milliequiv. per square meter per day in sodium intake, whereas retentions of 6 to 10 milliequiv. per kilogram have been noted after increases of approximately 250 milliequiv. per square meter per day in sodium intake.[22,31,36] The latter values are equivalent to 15 to 25 per cent of adult body sodium stores.[30,37]

Under conditions of acute illness, tendencies to retention of administered sodium may be increased, as stress, acting through the pituitary, prompts increased production of adrenocortical hormones.[38,39] In sick patients, therefore, stress may take such precedence over change in body sodium content in influencing the behavior of the adrenocortical-renal sodium excretion system as to favor excessive retention of salt and edema.

Patients who accumulate excessive amounts of sodium usually develop one or more of the symptoms and signs listed in Section D of Table 1.[14-17] Such signs develop when body sodium stores are increased above average normal levels by more than approximately 10 per cent. Surplus sodium may also displace potassium from body cells,[18,40] predisposing to the manifestations of potassium insufficiency listed in Section E of Table 1. Recognizing these facts, one group of clinical investigators has recommended that patients under stress be given not more than about 180 milliequiv. of sodium per square meter per day,[18] and another group has urged that total sodium intake be kept below the even more rigorous limit of 50 milliequiv. per square meter per day.[16]

On the basis of present information, 250 milliequiv. per square meter per day seems a reasonable estimate of the upper limit of short-term body tolerance for sodium of a patient under stress. This is indicated by Curve E-E of Figure 1.

Figure 1 suggested that it may not be possible to meet the minimum water needs (Curve B-B) of sick patients with isotonic (0.85 gm. per 100 cc. or 300 m-osm. per liter) saline solution without exceeding this limit of tolerance for sodium. Moreover, the figure calls attention to the fact that patients under stress given isotonic saline solution may become edematous even when the quantity administered is insufficient to satisfy minimum urine and insensible water requirements (see the V-shaped area lying beneath Curve B-B and to right of Curve E-E). Dilution of isotonic saline solution to one-half or one-third strength with dextrose solution largely eliminates this difficulty. Only about 2

liters of the former or about 1.5 liters of the latter type of fluid per square meter per day are needed to equalize minimum water losses of stressed patients (Curve B-B).

Potassium Homeostasis

The principles employed in estimating homeostatic limits of tolerance for potassium intake are basically the same as those used above for sodium. Body potassium content and serum potassium concentration homeostasis appear to be accomplished largely through the actions of the adrenocortical-renal system.[1]

Except under conditions of circulatory and renal insufficiency the limits of intake that may be considered compatible with body potassium homeostasis are thought to be approximately the same as those described above for sodium — namely, 10 to 250 milliequiv. per square meter per day.[19,22,23,41,42] Abrupt loading experiments have shown that healthy people can increase their rate of urinary potassium elimination from ordinary levels of 50 or 60 milliequiv. per square meter per day to 200 milliequiv. within a period of three hours.[41]

The effects of stress upon body tolerances for potassium are quite different from those described above for sodium. With stress increased production of adrenocortical hormones acts to facilitate potassium excretion by the kidneys.[1,20] Under conditions of reasonably good circulatory and renal efficiency, this can lead to marked depletion of body potassium stores, especially when the intake of sodium is overly generous and that of potassium is poor.[1,18-20,43,44] The salient clinical manifestations of this state are outlined in Section E of Table 1.[18-20]

When stress leads to circulatory collapse, with shock and marked oliguria or anuria, bodily capacity to distribute and excrete administered potassium becomes markedly impaired,[1,19,33] and even small doses of potassium may accumulate in the blood stream in toxic concentration. The clinical and laboratory changes that result are listed in Section F of Table 1.[19,21]

Comments on Sodium and Potassium Homeostasis

The manner in which patients may repair sodium and potassium deficits while receiving treatment that falls within the homeostatic limits of tolerance of Figure 1 is exemplified by the metabolic data of Figure 2. The 2 subjects of these studies were suffering from dehydration and acidosis as a result of diabetic ketosis. The heavily lined areas indicate the respective rates at which sodium and potassium were administered. The lightly shaded

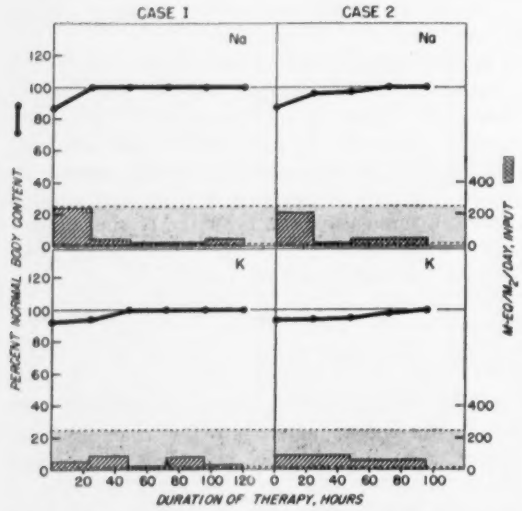

FIGURE 2. *Restoration of Body Sodium and Potassium Content to 100 Per Cent "Normal" by 2 Patients with Diabetic Acidosis. Throughout the three days of therapy, these patients were given sodium and potassium at rates that fell within the limits of homeostatic capacity. The light horizontal shaded areas are as indicated by the suggested limits of tolerance for sodium and potassium. (Case 1 is based on Nabarro et al.[45]) Case 2 was studied by us.*

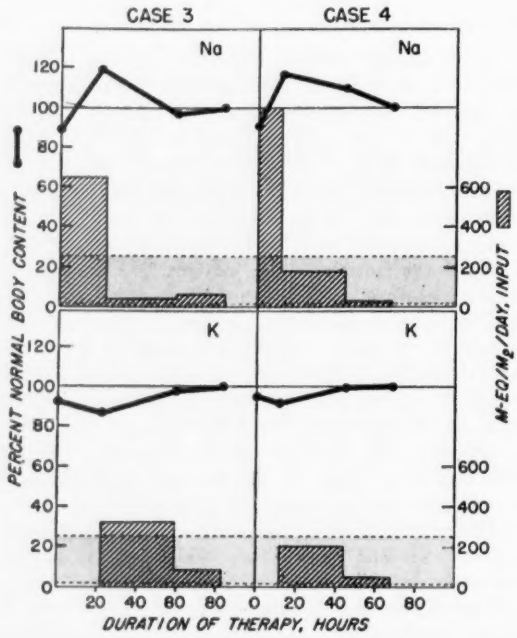

FIGURE 3. *Restoration of Body Sodium and Potassium Content to 100 Per Cent "Normal" by 2 Patients with Diabetic Acidosis (Based on Danowski et al.[43]).*

During the first twelve to twenty-four hours of therapy these patients were given sodium at rates considerably in excess of the upper limit of tolerance indicated in Figure 2. In addition potassium was withheld initially.

zones outlined by interrupted horizontal lines running across these areas correspond to the limits of homeostatic capacity mentioned above. The series of points connected by a solid line show the changes in body sodium and potassium content that occurred during the first three days of treatment. In plotting these data, we assumed that the sodium and potassium content, respectively, of each patient had become restored to approximately normal levels of about 45 milliequiv. per kilogram of body weight[46] by the end of the study. Percentage deviations from these values were then calculated from metabolic-balance data. It can be seen that the apparent sodium and potassium deficits of these patients were repaired in a smooth, asymptotic manner.

Figure 3 describes the response of 2 patients suffering from the dehydration of diabetic acidosis whose treatment during the first day of therapy fell outside the limits indicated above. During that day both patients received large amounts of sodium, but no potassium. In subsequent days the dosage of sodium was considerably reduced, and appreciable quantities of potassium were given. In these patients values of body sodium content swung from a position of deficit to an equally abnormal position of surplus in the first day of treatment. Values for potassium content fell slightly during the first day when the sodium intake was large and the potassium intake nil, but rose rapidly during the subsequent days when the patient was treated with potassium as well as with lesser amounts of sodium. Until it can be shown that the types of change demonstrated in Figure 3 are advantageous to the patient, it appears preferable to strive for the type of recovery illustrated in Figure 2.

Phosphorus Homeostasis

With the aid of the parathyroid-renal system, normal persons are able to keep values for serum inorganic phosphorus concentration within normal limits, if the phosphorus intake is not less than about 10 millimols (300 mg.) or more than about 65 millimols (2000 mg.) per square meter per 24 hours.[1,47] After an abrupt change in phosphorus intake one or two days are required for normal persons to complete homeostatic adjustments in urinary phosphorus excretion.[47]

Inadequate intake of phosphorus results in a tendency to hypophosphatemia. Although extreme degrees of hypophosphatemia are encountered quite often in patients recovering from diabetic acidosis, hypophosphatemia per se does not seem to give rise to any clearly defined clinical symptoms or disturbance in cellular or carbohydrate metabolism (Section G, Table 1).[1, 20, 22, 23] The administration of more phosphorus than the body can satisfactorily handle leads to hyperphosphatemia, hyperphosphaturia and other changes, some of which are listed in Section H of Table 1.[1]

Dextrose Homeostasis

The ketonuria of fasting can be eliminated, and the losses of nitrogen and electrolytes incident to starvation can be minimized by the administration of about 75 gm. of dextrose per square meter per day.[5,6] This quantity corresponds closely to the obligatory metabolic requirements for carbohydrates of the nervous system.[48,49]

The upper limit of tolerance for dextrose is taken as approximately 300 gm. per square meter per

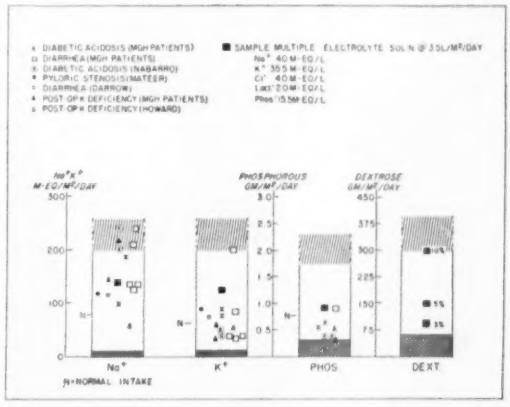

FIGURE 4. *Minimum Requirement and Maximum Tolerance for Sodium, Potassium, Phosphate and Dextrose.*

The height of the heavily cross-hatched area at the bottom of each column represents the value for minimum need, and the total height of each column indicates the value for maximum tolerance for the substance as discussed in the text. The top of each column is shown as a zone rather than a solid line to indicate that there is no sharp dividing line between quantities that are physiologically tolerable and those that are excessive and toxic. The various symbols show the rate at which the substance in question was administered during the first day of intravenous therapy to patients with the conditions indicated. The solid black squares indicate the rate at which sodium, potassium and phosphorus are being given when the sample multiple electrolyte solution is infused at a rate of 3.5 liters per square meter per day. Administration of this solution at more and less rapid rates, respectively, leads to proportional upward and downward shifts in the position of these black squares.

twenty-four hours. The administration of dextrose to dogs at more rapid rates leads to hepatomegaly, signs of liver failure and, eventually, hyperglycemia and death.[24] The rapidity with which these changes develop depends upon the extent to which the foregoing "ceiling value" for dextrose tolerance is exceeded. Dextrose given at a rate of approximately 1000 gm. per square meter per twenty-four hours kills dogs within a few hours. Intermediate doses have caused death to occur within periods of three to twenty-five days.

DISCUSSION

As outlined above, it appears possible to indicate at least approximately the limits of capacity of the systems concerned with body-water, sodium, potassium, phosphate and dextrose homeostasis. Under

circumstances where the homeostatic systems are functioning normally and when these substances are administered at rates that fall within the capacity of hemostatic function, one can expect patients to retain or reject these substances in accordance with current needs. The ability to meet all types of circumstances as they arise will, of course, be greatest when water and solutes are given at rates that are appreciably above the lower and below the upper limit of tolerance for the particular substance.

One can conceive of a number of solutions that, infused at appropriate rates, should occupy such a middle position. A sample solution of this type, currently under investigation on this service, is indicated in Figure 4. If this solution is administered at a rate of 3.5 liters per square meter per twenty-four hours, electrolytes, dextrose and water will be delivered as indicated by the respective positions of the black squares of Figures 4 and 5.

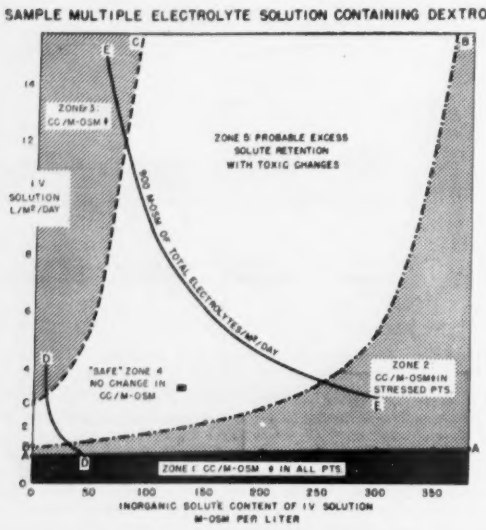
SAMPLE MULTIPLE ELECTROLYTE SOLUTION CONTAINING DEXTROSE
ZONE 5 CC/M-OSM ∞
ZONE 5 PROBABLE EXCESS SOLUTE RETENTION WITH TOXIC CHANGES
I V SOLUTION L/M²/DAY
900 MOSM OF TOTAL ELECTROLYTES/M²/DAY
"SAFE" ZONE 4 NO CHANGE IN CC/M-OSM
ZONE 2 CC/M-OSM⊖IN STRESSED PTS.
ZONE 1 CC/M-OSM ∞ IN ALL PTS.
0 50 100 150 200 250 300 350
INORGANIC SOLUTE CONTENT OF I V SOLUTION M-OSM PER LITER

FIGURE 5. *Minimum Requirement and Maximum Tolerance for the Sample Multiple Electrolyte Solution Described in Figure 4. Administration of this solution at a rate of 3.5 liters per square meter per twenty-four hours places the patient in the position indicated by the black square located near the center of zone 4. (See text for descriptive comments.)*

Each of the other points of the various symbols plotted in Figure 4 represents the rates at which sodium, potassium and phosphate were administered during the first day of treatment to patients suffering, respectively, from dehydration with alkalosis due to vomiting,[50] alkalosis secondary to postoperative potassium deficiency,[22, 51] dehydration with acidosis resulting from diarrhea[22, 52*] or diabetic acidosis and dehydration.[22, 25, 45] Since all the patients recovered while receiving this therapy, the rates of administration shown must have been sufficient to meet not only normal but also the additional abnormal maintenance and repair requirements imposed by the disease condition. Such data suggest that when an appropriate potassium intake is provided it may seldom be necessary to administer more than about 150 milliequiv. of sodium per square meter per day to sick, depleted patients.

Figure 5 is constructed similarly to Figure 1 except that the inorganic solute content is composed of multiple electrolytes as depicted in Figure 4 instead of simply sodium chloride as in Figure 1. Thus line E-E in Figure 5 represents the limits of tolerance for the total electrolytes of such a solution. An infusion rate of 3.5 liters per square meter per day provides the water and various solutes of this solution at rates approximately midway between values for minimum need and maximum tolerance. In this connection, it is to be emphasized that there is no intention to recommend this particular solution or this particular rate of administration. For instance, it is appreciated that it may ultimately prove advantageous to include such intracellular nutrients as magnesium, sulfate and amino acids. Experience, however, has revealed that 2 liters per square meter per day of the solution described here is ample for patients who simply require maintenance therapy, whereas more than 3.5 liters per square meter per twenty-four hours is seldom necessary even for patients with large deficits or continuing losses.

There are certain conditions that may limit the body's ability to utilize such multiple electrolyte solutions safely and advantageously. The homeostatic limitations of newborn infants and of patients suffering from advanced nephritis, cardiac failure, Addison's disease, diabetes insipidus and hypoparathyroidism are well known. Moreover, the special problems in such cases indicate the difficulties encountered when the patient is dependent upon the wisdom of the physician rather than that of the body.

A somewhat more common limitation is apt to occur during periods when patients are under the influence of morphine and its derivatives or the barbiturates.[53, 54] These agents stimulate the posterior pituitary gland to secrete antidiuretic hormone regardless of bodily needs for water elimination. As a consequence, there may be a temporary loss of ability to increase urine water concentration above relatively low values. Substitution of a representative value such as 2 cc. per milliosmol for α in the formula presented above in connection with Figure 1 yields a line that falls slightly below Curve B of Figures 1 and 5. This means that under these circumstances administration of dextrose in water solution at a rate of more than approximately

*In these patients, the value is that reported for the first two-day or three-day period of therapy. As with the other data, the data are expressed on a basis of square meter per day.

1100 cc. per twenty-four hours (45 cc. per hour) per square meter may induce water intoxication. For instance, the administration of 2 liters per square meter for twenty-four hours would result in a 5 per cent increase in the body-water concentration of a person weighing 30 kg. — an increase sufficient to produce signs of toxicity. This risk of water intoxication, which is greatest when plain dextrose and water solutions are used, may be reduced to small proportions by the addition of 100 or more m-osm. of inorganic solute (for example, 50 milliequiv. of total base) to each liter of solution.

Finally, patients often suffer temporary impairment of homeostatic function as a result of marked dehydration with reduction of circulatory and renal efficiency. In such cases it is our custom at present to postpone use of multiple electrolyte solution until the patient's circulatory and renal efficiency has been at least partially restored by means of a simple saline and dextrose infusion. Ordinarily, one can accomplish this within one or two hours by administering at a rate of about 8 cc. per square meter per minute a solution made up of four parts of 5 per cent dextrose in water plus six parts of 5 per cent dextrose in 0.85 gm. per 100 cc. of saline solution. This solution contains per liter 90 milliequiv. of sodium and 90 milliequiv. of chloride or a total of 180 m-osm. of inorganic solute. Under circumstances of anemia or hypoproteinemia, a transfusion of 300 cc. per square meter may also be indicated.

Summary and Conclusions

The limits of capacity of the body's homeostatic systems to conserve and to eliminate water, sodium, potassium, phosphate and glucose are described in approximate terms with the aid of diagrams. Consideration of these limits and of the effects of exceeding them in parenteral fluid therapy leads to the following conclusions:

Simple dextrose solutions are apt to induce water intoxication in anyone if given more rapidly than 2700 cc. per square meter per twenty-four hours (110 cc. per square meter per hour). The danger of inducing water intoxication is increased considerably when patients are given such commonly used drugs as morphine or its derivatives or barbiturates. Under this circumstance tolerance for simple dextrose solution may be reduced to 1100 cc. per square meter per twenty-four hours. The addition of as little as 80 m-osm. of inorganic solute (for example, 40 milliequiv. of total base) per liter of dextrose solution will increase tolerance severalfold.

Isotonic saline in dextrose solution is incapable of causing water intoxication. On the other hand, this solution is so rich in inorganic solutes and so poor in physiologically free or available water that as much as 5 liters per square meter per twenty-four hours may be required to meet the minimum maintenance water requirements of patients under severe stress. The administration of this much sodium chloride (43 gm. or 750 milliequiv. per square meter per day) is apt to induce excessive edema formation. In fact, patients under severe stress given isotonic saline solution can paradoxically show excess sodium chloride and water retention (edema formation) while suffering at the same time from water deficit as evidenced by hypertonicity of body fluids and oliguria.

The difficulties inherent in the parenteral use of either solutions of dextrose in water or dextrose in isotonic saline can be reduced by the use of one-half to two-thirds isotonic saline in dextrose solution (that is, two parts of dextrose in saline solution plus either one or two parts of dextrose in water). Such solutions appear suitable for the initial hydration of most severely sick patients. However, these solutions are inadequate for prolonged therapy because they lack ions essential for repair of intracellular deficits.

Solutions containing intracellular (K, PO_4) as well as extracellular (Na, Cl, HCO_3) ions in physiologically tolerable amounts can easily be constructed. The results obtained to date by infusion of hypotonic multiple electrolyte solutions at rates of from 1.5 to approximately 3.5 liters per square meter per twenty-four hours suggest that they may have wide usefulness in helping patients with basically normal endocrine-renal homeostatic systems to cure themselves of disturbances in fluid and electrolyte metabolism.

Although the limitations in the use of such solutions in the treatment of patients with marked reduction in homeostatic function remain to be defined, the application of the principles considered in this paper to the parenteral and dietary therapy of patients with severe limitation in renal function should be apparent.

References

1. Talbot, N. B., Sobel, E. H., McArthur, J. W., and Crawford, J. D. *Functional Endocrinology from Birth through Adolescence.* 638 pp. Cambridge, Massachusetts: Harvard University Press, 1952.
2. Heeley, A., and Talbot, N. B. Unpublished data.
3. Newburgh, L. H., Johnston, M. W., and Newburgh, J. D. *Some Fundamental Principles of Metabolism.* 63 pp. Ann Arbor: Edwards Brothers, Incorporated, 1945.
4. Newburgh, L. H., and Johnston, M. W. Insensible loss of water. *Physiol. Rev.* **22**:1-18, 1942.
5. Gamble, J. L. Physiological information gained from studies on life raft ration. In *The Harvey Lectures.* 331 pp. Lancaster, Pennsylvania: The Science Press Printing Company, 1946-1947. Pp. 247-273.
6. Butler, A. M., Talbot, N. B., MacLachlan, E. A., Appleton, J. E., and Linton, M. A. Effect of testosterone propionate on losses incident to inadequate dietary intake. *J. Clin. Endocrinol.* **5**:327-336, 1945.
7. Gamble, J. L., and Butler, A. M. Measurement of renal water requirement. *Tr. A. Am. Physicians* **58**:157-161, 1944.
8. Barnett, H. L., Vesterdahl, J., McNamara, H., and Lauson, H. D. Renal water excretion in premature infants. *J. Clin. Investigation* **31**:1069-1073, 1952.
9. Nadal, J. W., Pedersen, S., and Maddock, W. G. Comparison between dehydration from salt loss and from water deprivation. *J. Clin. Investigation* **20**:691-703, 1941.
10. Elkinton, J. R., Danowski, T. S., and Winkler, A. W. Hemodynamic changes in salt depletion and in dehydration. *J. Clin. Investigation* **25**:120-129, 1946.
11. Weir, J. F., Larson, E. E., and Rowntree, L. G. Studies in diabetes insipidus, water balance and water intoxication. *Arch. Int. Med.* **29**:306-338, 1922.

12. Rowntree, L. G. Effects on mammals of administration of excessive quantities of water. *J. Pharmacol. & Exper. Therap.* **29**:135-159, 1926.

13. Smyth, F. S., Deamer, W. C., and Phatek, N. M. Studies in so-called water intoxication. *J. Clin. Investigation* **12**:55-65, 1933.

14. Cutting, R. A., Larson, P. S., and Lands, A. M. Cause of death resulting from massive infusions of isotonic solutions: experimental study. *Arch. Surg.* **38**:599-616, 1939.

15. Coller, F. A., Campbell, K. N., Vaughan, H. H., Iob, V., and Moyer, C. A. Postoperative salt intolerance. *Ann. Surg.* **119**:533-542, 1944.

16. Elman, R., Lemmer, R. A., Weichselbaum, T. E., Owen, J. G., and Yore, R. W. Minimum postoperative maintenance requirements for parenteral water, sodium, potassium, chloride and glucose. *Ann. Surg.* **130**:703-722, 1949.

17. Ariel, I. M., and Kremen, A. J. Compartmental distribution of sodium chloride in surgical patients pre- and postoperatively. *Ann. Surg.* **132**:1009-1026, 1950.

18. Moore, F. D., and Ball, M. R. *The Metabolic Response to Surgery.* 167 pp. Springfield, Illinois: Charles C Thomas, 1952.

19. Elkington, J. R., and Tarail, R. Present status of potassium therapy. *Am. J. Med.* **9**:200-207, 1950.

20. Eliel, L. P., Pearson, O. H., and Rawson, R. W. Postoperative potassium deficit and metabolic alkalosis. *New Eng. J. Med.* **243**: 471-478 and 518-524, 1950.

21. Darrow, D. C., and Pratt, E. L. Fluid therapy: relation to tissue composition and expenditure of water and electrolyte. *J. A. M. A.* **143**:365-373 and 432-439, 1950.

22. Research Staff, Children's Medical Service, Massachusetts General Hospital. Unpublished data.

23. Butler, A. M. Diabetic coma. *New Eng. J. Med.* **243**:648-659, 1950.

24. Astwood, E. B., Flynn, J. M., and Krayer, O. Effect of continuous intravenous infusion of glucose in normal dogs. *J. Clin. Investigation* **21**:621, 1942.

25. Butler, A. M., Talbot, N. B., Burnett, C. H., Stanbury, J. B., and MacLachlan, E. A. Metabolic studies in diabetic coma. *Tr. A. Am. Physicians* **60**:102-109, 1947.

26. Hinkle, L. E., Jr., Edwards, C. J., and Wolf, S. Occurrence of diuresis in humans in stressful situations and its possible relation to diuresis of early starvation. *J. Clin. Investigation* **30**:809-817, 1951.

27. Crawford, J. D. Unpublished observations.

28. Crawford, J. D., Schoen, E., and Nicosia, A. P. Factors determining maximum renal water excretion capacity. *Am. J. Dis. Child.* **83**: 91, 1952.

29. Smith, H. W. *The Physiology of the Kidney.* 310 pp. New York: Oxford University Press, 1937.

30. Shohl, A. T. *Mineral Metabolism.* 384 pp. New York: Reingold, 1939.

31. Leaf, A., and Couter, W. T. Evidence that renal sodium excretion by normal subjects is regulated by adrenal cortical activity. *J. Clin. Investigation* **28**:1067-1081, 1949.

32. Leaf, A., Couter, W. T., and Newburgh, L. H. Some effects of variation in sodium intake and of different sodium salts in normal subjects. *J. Clin. Investigation* **18**:1082, 1949.

33. Cutler, H. H., Power, M. H., and Wilder, R. M. Concentrations of chloride sodium and potassium in urine and blood: their diagnostic significance in adrenal insufficiency. *J. A. M. A.* **111**:117-122, 1938. Concentrations of sodium, chloride and potassium in blood plasma and urine of patients with Addison's disease: their diagnostic significance. *Proc. Staff Meet., Mayo Clin.* **13**:244-249, 1938.

34. Elkington, J. R., and Taffel, M. Prolonged water deprivation in dog. *J. Clin. Investigation* **21**:787-794, 1942.

35. Locke, W., Talbot, N. B., Jones, H. S., and Worcester, J. Studies on combined use of measurements of sweat electrolyte composition and rate of sweating as index of adrenal cortical activity. *J. Clin. Investigation* **30**:325-337, 1951.

36. Stewart, J. D., and Rourke, G. M. Effects of large intravenous infusions on body fluid. *J. Clin. Investigation* **21**:197-205, 1942.

37. Forbes, G. B., and Perley, A. Estimation of total body sodium by isotopic dilution. II. Studies on infants and children: example of constant differential growth ratio. *J. Clin. Investigation* **30**: 566-574, 1951.

38. Selye, H. General adaptation syndrome and diseases of adaptation. *J. Clin. Endocrinol.* **6**:117-230, 1946.

39. Johnson, H. T., Conn, J. W., Iob, L. V., and Coller, F. A. Postoperative salt retention and its relation to increased adrenal cortical function. *Ann. Surg.* **132**:374-385, 1950.

40. Darrow, D. C., and Miller, H. C. Production of cardiac lesions by repeated injections of desoxycorticosterone acetate. *J. Clin. Investigation* **21**:601-611, 1942.

41. Keith, N. M., and Osterberg, A. E. Human tolerance for potassium. *Proc. Staff Meet., Mayo Clin.* **21**:385-392, 1946.

42. Gamble, J. L., et al. Effects of large loads of electrolytes. *Pediatrics* **7**: 305-320, 1951.

43. Danowski, T. S., Peters, J. H., Rathbun, J. C., Quashnock, J. M., and Greenman, L. Studies in diabetic acidosis and coma, with particular emphasis on retention of administered potassium. *J. Clin. Investigation* **28**:1-9, 1949.

44. Berry, R. E. L., Iob, V., and Campbell, K. N. Potassium metabolism in immediate postoperative period. *Arch. Surg.* **57**:470-478, 1948.

45. Nabarro, J. D. N., Spencer, A. G., and Stowers, J. M. Metabolic studies in severe diabetic ketosis. *Quart. J. Med.* **21** (N.S.) **57**: 225-248, 1952.

46. Forbes, G. B. Chemical growth in infancy and childhood. *J. Pediat.* **41**:202-232, 1952.

47. Crawford, J. D., Osborne, M. M., Jr., Talbot, N. B., Terry, M. L., and Morrill, M. F. Parathyroid glands and phosphorus homeostasis. *J. Clin. Investigation* **29**:1448-1461, 1950.

48. Scheinberg, P., and Stead, E. A., Jr. Cerebral blood flow in male subjects measured by nitrous oxide technique. Normal values for blood flow, oxygen utilization, glucose utilization and peripheral resistance, with observations on effect of tilting and anxiety. *J. Clin. Investigation* **28**:1163-1171, 1949.

49. Myers, J. D., Brannon, E. S., and Holland, B. C. Correlative study of cardiac output and the hepatic circulation in hyperthyroidism. *J. Investigation* **29**:1059-1077, 1950.

50. Mateer, F. M., et al., Use of potassium chloride in preoperative treatment of pyloric stenosis in infants. *Am. J. M. Sc.* **221**:21-27, 1951.

51. Howard, J. E., and Carey, R. A. Use of potassium in therapy. *J. Clin. Endocrinol.* **9**:691-713, 1949.

52. Darrow, D. C., Pratt, E. L., Flett, J., Jr., Gamble, A. H., and Wiese, H. F. Disturbances of water and electrolytes in infantile diarrhea. *Pediatrics* **3**:129-156, 1949.

53. deBodo, R. C. Antidiuretic action of morphine, and its mechanism. *J. Pharmacol. & Exper. Therap.* **82**:74-85, 1944.

54. deBodo, R. C., and Prescott, K. F. Antidiuretic action of barbiturates (phenobarbital, amytal, pentobarbital) and a mechanism involved in this action. *J. Pharmacol. & Exper. Therap.* **85**:222-233, 1945.

MEDICAL INTELLIGENCE

DEATH ASSOCIATED WITH HEXAMETHONIUM AND 1-HYDRAZINOPHTHALAZINE (APRESOLINE) THERAPY*

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BOSTON

HEXAMETHONIUM, a ganglionic blocking agent,[1] has recently been introduced in the therapy of hypertension. The effectiveness of sympathetic blockade determines its hypotensive properties; the undesirable side effects result, for the most part, from blockade of parasympathetic ganglions. The present report describes a fatal case that followed hexamethonium administration; the concurrent use of another new hypotensive drug, 1-hydrazinophthalazine (Apresoline) probably militated against successful correction of the autonomic derangement consequent to hexamethonium.

CASE REPORT

P. T. (M 37633), a 56-year-old woman, was admitted to the Beth Israel Hospital on January 23, 1953, because of suspected acute mesenteric thrombosis. She had had hypertension (blood pressure of 240-250 systolic, 100-110 diastolic) for 8 years, and had had an episode of prolonged chest pain 5 years before admission followed by angina pectoris. Because of severe headaches and persistent hypertension, hexamethonium chloride administration was begun 5 months before admission. The initial dosage of 125 mg. orally 4 times daily was gradually increased to 500 mg. orally 4 times daily 3 months before admission. 1-hydrazinophthalazine was added 1 month before admission, at first in a dosage of 10 mg. orally 4 times daily, with a gradual increase to 25 mg. 4 times daily 3 weeks before entry. However, monthly blood-pressure determinations were never below 220/90 in the supine or 200/90 in the sitting position. Concurrently, digitalis leaf, 0.1 gm. by mouth daily, and phenobarbital, 15 mg. 4 times a day, had been administered. During these 5 months, there was no syncope, dizziness, incontinence, urinary retention or constipation.

For 2 days before admission the patient had had no bowel movement. The last dose of both drugs had been taken 16 hours before entry. On the evening before admission, she experienced mild abdominal distress. Several hours later she was awakened from sleep by severe abdominal pain, marked dizziness and a sensation of "blacking out." An enema yielded a yellow, formed stool, which was followed by diarrheal movements and, subsequently, by incontinence of feces. No bloody or tarry material was noted in the stool. Her physician found the blood pressure to be 80/50. At no time did she have chest pain, sweating, cough, dyspnea or cyanosis.

Physical examination revealed an obese, lethargic, acutely ill woman. There was no pallor, cyanosis or sweating. There were no external signs of cranial injury. The pupils were of moderate size, round and equal, and did not react to light. Extraocular movements were normal. The fundi showed only arteriosclerotic vessel changes. There was no facial asymmetry, and the tongue protruded in the midline. The neck was supple; the cervical veins were not distended. The lungs were clear. The heart was slightly enlarged, and the cardiac sounds inaudible. The abdomen was obese and doughy; no masses or organs could be felt. There was a mild generalized tenderness, but no rigidity or spasm; peristaltic sounds were absent. The peripheral pulsations were all palpable. The cranial nerves were normal, and the deep tendon reflexes equal. Babinski and Hoffmann signs were absent.

The blood pressure was 50/30. The temperature was 101°F., the pulse 46, and the respirations 20.

Examination of the blood disclosed a hemoglobin of 16 gm. per 100 cc. and a white-cell count of 16,000; the serum amylase was 124 units, and the nonprotein nitrogen 52 mg. per 100 cc. An electrocardiogram showed sinoauricular bradycardia with a rate of 50, marked left-axis deviation and a PR interval 0.28 second. The T waves were inverted in Leads I and aVL. There were notched R waves of small amplitude in V_6.

The patient was immediately placed in the Trendelenburg position and given a rapid intravenous infusion of 5 per cent dextrose in water containing 4 microgm. of nor-epinephrine per cubic centimeter (1 ampoule of 4 mg. per liter). The blood pressure rose transiently to 70/50, and the heart rate to 60. Soon after admission she vomited brown, guaiac-negative, fecal-smelling material. Fecal incontinence continued; the stools were brown and guaiac negative. A roentgenogram of the abdomen showed a moderate amount of gas in the small and large bowel. After an unsuccessful attempt to pass a Harris tube, a Levin tube was passed, and 600 cc. of brown material with a fecal odor was obtained by suction during the next 12 hours. Catheterization of the bladder yielded 30 cc. of urine shortly after admission and none thereafter.

No further response to the initial dosage of nor-epinephrine was observed, and the concentration was raised to 32 microgm. per cubic centimeter, with no additional blood-pressure response. Prostigmine, 1 mg. intramuscularly every hour, was started to stimulate peristalsis. Despite these measures, the patient became progressively less responsive, comatose and tachypneic. The blood pressure became unobtainable 14 hours after admission, and she died 1 hour later. At no time during the hospital stay were any peristaltic sounds heard, nor was any sweating noted. The pupils remained unreactive to light, and the blood pressure never rose above 70/50. The clinical diagnoses were paralytic ileus and shock due to hexamethonium.

At post-mortem examination§ 10 hours after death, the peritoneal cavity contained 10 cc. of clear, yellow fluid. All the abdominal viscera except the small bowel were normal. The small bowel from duodenum to ileocecal valve was markedly distended; the maximum diameter was 4 cm. The celiac, inferior and superior mesenteric arteries were injected with radiopaque mass and dissected with the aid of roentgenograms.[2] No narrowings or occlusions were noted in either the major vessels or their branches. Sections of the small bowel showed an edematous submucosa with infiltration by polymorphonuclear leukocytes. Connected to the mucosa by pin-point attachments was a pseudomembrane¶ composed of round and epithelial cells. Sections from the descending colon demonstrated numerous polymorphonuclear leukocytes in the submucosa and the muscularis.

The lungs showed moderate pulmonary edema, congestion and focal atelectasis, most marked in the right lower lobe. The pulmonary vessels were free of thrombi.

The heart weighed 520 gm. Dissection of the coronary vessels by the Schlesinger method[4] revealed several arteriosclerotic narrowings of both coronary arteries and a complete old oc-

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¶The pseudomembrane may have been related to the prolonged period of shock before death.[3]

clusion at the origin of the septal branch of the right coronary artery. Sections of the myocardium disclosed only hypertrophy of the fibers and some increase in acellular fibrous tissue in the septums.

Examination of the brain was not performed.

The final autopsy diagnoses were paralytic ileus of the small intestine; pseudomembranous enteritis; interstitial inflammation of the descending colon; cardiac hypertrophy; coronary arteriosclerosis, with a single old occlusion; myocardial fibrosis, mild; and congestion and edema of the lungs and atelectasis of the right lower lobe.

Discussion

The development of paralytic ileus and shock was consistent with hexamethonium toxicity. Since a significant portion of the ingested drug is excreted in the feces,[5] the absence of normal bowel movements for two days favored increased absorption of the drug.[6] The clinical syndrome of hexamethonium poisoning appears to be quite specific, with 5 reports[7-11] showing features almost identical to those in the case described above. The sequence of constipation, paralytic ileus and shock was present in all. In these 5 cases death resulted from paralytic ileus.[7-11] Postmortem examinations showed, as in our patient, only gastrointestinal distention. It appears that 1-hydrazinophthalazine can be excluded as a cause of the development of paralytic ileus.[12] However, the shock observed in the patient may have been related to the combined action of hexamethonium and 1-hydrazinophthalazine.

The syndrome of hexamethonium-induced paralytic ileus must be considered in the differential diagnosis of intestinal obstruction and shock. In several reported cases, the diagnosis of intestinal obstruction due to internal herniation or mesenteric thrombosis has led to unnecessary operation. Similarly, a surgical consultant who saw our patient believed the diagnosis to be acute mesenteric thrombosis and advised that operation be undertaken as soon as the patient's condition permitted. The unreactive pupils and the lack of sweating, however, indicated the effects of a powerful parasympathetic blocking agent. The absence of blood in the stool was also helpful in indicating the correct clinical diagnosis.

It appears that drug retention and toxicity may be avoided by the prevention of constipation. Cathartics or enemas should be instituted whenever a hexamethonium-treated patient has had no bowel movement for twenty-four hours. Although cholinergic drugs have been utilized for the alimentary-tract reactions, it should be emphasized that further lowering of the blood pressure by generalized vasodilatation may occur.

Effective countermeasures against the toxic hypotensive reactions to combined therapy have not been reported. Shock due to hexamethonium is counteracted by sympathomimetic drugs with pure vasoconstrictive action such as nor-epinephrine and phenylephrine (Neosynephrine). Epinephrine is contraindicated.[13] It is striking, however, that infusion of a high concentration (32 microgm. per cc.) of nor-epinephrine was unsuccessful in our patient. This may have been due to the previous administration of 1-hydrazinophthalazine. It has been demonstrated in animals that 1-hydrazinophthalazine in a limited dosage range inhibits the pressor response of nor-epinephrine.[14] No studies have been reported on this subject.

Since the absorbed hexamethonium[15] and possibly 1-hydrazinophthalazine[12] are excreted through the kidney, anuria maintains high plasma levels and perpetuates toxicity. Artificial dialysis was considered in the case reported above but was not instituted because of the critical clinical status. Information concerning the dialyzability of these drugs would be of interest in view of the serious nature of the toxic reactions.

When drugs with such potent side effects are used, physicians and patients should understand their mode of action and potential risk to prevent deaths such as that recorded above. In view of the diagnostic and therapeutic problems, it might be wise for patients receiving these drugs to carry a card indicating the drugs and dosages.

Summary and Conclusions

A fatal case of shock and paralytic ileus in a hypertensive patient treated with hexamethonium chloride and 1-hydrazinophthalazine (Apresoline) is reported. Differential diagnosis and corrective measures are briefly discussed.

Knowledge by physicians of the pharmacodynamic effects of these drugs is required; it is also necessary that patients be informed of the early side effects. Cathartics or enemas should be instituted when a patient under hexamethonium therapy has had no bowel movement for twenty-four hours.

References

1. Paton, W. D. M. Paralysis of autonomic ganglia, with special reference to therapeutic effects of ganglion-blocking drugs. *Brit. M. J.* **1**: 773-778, 1951.
2. Schlesinger, M. J. Unpublished data.
3. Penner, A., and Bernheim, A. I. Acute postoperative enterocolitis: study on pathologic nature of shock. *Arch. Path.* **27**:966-983, 1939.
4. Schlesinger, M. J. Injection plus dissection study of coronary artery occlusions and anastomoses. *Am. Heart J.* **15**:528-568, 1938.
5. Milne, G. E., and Oleesky, S. Excretion of methonium compounds. *Lancet* **1**:889, 1951.
6. Grimson, K. S., Orgain, E. S., Rowe, C. R., Jr., and Sieber, H. A. Caution with regard to use of hexamethonium and "apresoline." *J. A. M. A.* **149**:215-220, 1952.
7. Mackey, W. A., and Shaw, G. B. Paralytic ileus after hexamethonium. *Brit. M. J.* **1**:1205, 1951.
8. Bourne, G., and Hosford, J. Methonium compounds in hypertension. *Lancet* **1**:527, 1951.
9. Thomas, O., and Williams, R. G. Paralytic ileus after hexamethonium. *Brit. M. J.* **1**:1331, 1951.
10. Hirson, C., and Kelsall, A. R. Paralytic ileus after hexamethonium. *Brit. M. J.* **1**:1332, 1951.
11. Goldstone, B. Death associated with methonium treatment. *South African M. J.* **26**:552-554, 1952.

12. Schroeder, H. A. Control of hypertension by hexamethonium and 1-hydrazinophthalazine. *Arch. Int. Med.* **89**:523-540, 1952.
13. Freis, E. D., Finnerty, F. A., Jr., Schnaper, H. W., and Johnson, R. L. Treatment of hypertension with hexamethonium. *Circulation* **5**: 20-27, 1952.
14. Freis, E. D., MacKay, J. C., and Oliver, W. F. Effect of "sympatholytic" drugs on cardiovascular responses to epinephrine and norepinephrine in man. *Circulation* **3**:254-259, 1951.
15. Milne, G. E., and Oleesky, S. Absorption of hexamethonium. *Brit. M. J.* **2**:177, 1951.

BY THE LONDON POST

Medicine and Social Policy — Exhibition of Medical Photography — 25-Year Follow-up Report

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LONDON, ENGLAND

PRESENT-DAY discussions on medicine and social policy are so often clouded by the political aspects of the problem as they affect the doctor and his patients that it was refreshing to hear Professor F. A. E. Crew, F. R. S., treat the subject in a purely objective and philosophic manner in the Sir Charles Hastings Memorial Lecture at B. M. A. House.

Professor Crew traced the State's growing appreciation of its responsibility for the health of the people from the time that a commission was appointed in 1832 to enquire into the Poor Laws right up to the formation of the Ministry of Health in 1919 and the National Health Service Act of 1946. He showed how medicine had become separated into two great fields, the first being the province of the medical profession and concerning diagnosis, prognosis and treatment, and the second the province of local and central government and being chiefly concerned with public health and preventive medicine.

As the Government and the profession have realized the importance of preventive medicine, so have they realized the value of educating the people in ways of healthy living. It has been said that if health is every man's duty it must also be every man's quest, and Professor Crew stressed the fact that no government can impose a regimen of health on a disinterested population.

Sanitation, vaccination, immunization and, more recently, the antibiotic drugs have all helped to eliminate the great epidemic and infectious diseases, and this has been reflected in the Registrar General's statistics. In the last hundred years the crude death rate in Great Britain has been reduced by half, the mortality of children under ten reduced to less than a sixth and the normal life expectancy increased from forty to sixty-five years.

On the other hand, this conquest of infectious disease has brought other conditions forward as the major causes of death: cardiovascular disease now accounts for a third of all the deaths, and cancer, violence and tuberculosis together claim an equal number. Another group of diseases that have come forward are those which Professor Crew considers to represent "symbolic sickness." He suggested that man's development from the primitive to the modern has necessitated a reorientation, of which all have not been equally capable. Thus, the symbolic sickness or psychosomatic diseases have appeared and represent the "dramatized discontent borne of disharmony, the malaise of maladjustment."

Professor Crew thought it would be calamitous to rob man of the luxury of these diseases because for some there is no escape from the modern world except by the narrow neck of the medicine bottle. He suggested that health is partly a matter of the spirit of man and represents a state of harmony within oneself and between oneself and the external world.

Finally, he stressed the medical advances of the century that have led to a rising mean age of the population. Society's will is that life should be prolonged and if the quest for knowledge into vascular and neoplastic disease is successful, the span of life may be extended even farther. If this occurs the differences between chronologic age and physiologic age will need to be adjusted, and Professor Crew thought that as a counterpart to the child-guidance clinic, which teaches one how to enter the stage, a senescence-guidance clinic will be needed to teach one how to leave!

* * *

The Royal Photographic Society has just held, as part of its centenary celebration, an exhibition of medical photography. Historically, the use of the camera in medicine is interesting, and although I mention his name with great trepidation (since once more it seems to be in connection with some kind of record) it was apparently William Cheselden who was one of the earliest members of the profession to use any form of camera. The *Oxford English Dictionary* gives 1727 as the earliest date of any reference to the camera obscura. In Cheselden's famous book, *Osteographia, or the Anatomy of the Bones* (London, 1733) the frontispiece shows Cheselden seated at this instrument drawing a skeleton hanging from a tripod. A later page of the text then describes the instrument as follows:

> About six inches within that end where the draftsman sits, is fixed the table glass, upon the rough side of which he draws with a black-lead pencil, which he afterwards traces off upon paper, towards the other end, in a sliding frame, is put the object-glass, which being moved backward or forward, makes the picture bigger or less, and the inside of the case is made black to prevent reflections of light.

The recent exhibition was designed to illustrate how the great advances in photography since the days of this pioneer instrument have been used in the medical photographic department. The ideal hospital department was described, and exhibits included reproductions of radiographs, retinal photographs, photomicrography, and demonstrations of the technic for endoscopic and intraperitoneal photography. It was urged that more use should be made of the medical photographer in the belief that many doctors seem unaware of the many ways in which he can help in the recording of cases.

* * *

In the years 1923-1926, 899 medical students graduated from the University of Glasgow, and all those still alive in 1950 received a questionnaire from some of their number who thought it would be interesting to make a twenty-five-year follow-up study of their contemporaries. The results of this questionnaire were presented in 1951 at a reunion that celebrated the quin-centenary of the university's foundation. Meiklejohn* has just presented a full analysis of the results.

Of the 800 graduates who had survived the quarter century, 385 returned the questionnaire with answers to 25 searching questions on their life and opinions; 59 per cent were in general practice, and 18 per cent had become consultants. In spite of Dr. Johnson's dictum that the fairest prospect for a Scot is the broad highway to England, 40 per cent of the doctors in the group were still in Scotland, with 52 per cent in England and Wales and 8 per cent abroad. Three quarters were married within ten years of graduation, and 90 per cent by the time of the inquiry.

Concerning their health, 50 per cent stated that they had had no serious illness since graduating, and of those who had suffered illness, the predominance was of gastrointestinal affections, appendicitis, cholecystitis and peptic ulcer being most common. The only statistically significant cause of death among the 99 who had died was violence. Excluding 5 war casualties, there were 20 deaths from this cause (violence, 7, drowning, 5, and poisoning, 8). The total number of deaths from heart disease was not significantly raised, but the number certified as due to coronary thrombosis (9) seemed high.

Almost all the doctors had found medicine a satisfying way of life and the *British Medical Journal* has suggested that it would be interesting if other medical schools made follow-up investigations among their old students, so that a real picture could be built up of the doctor as a man and a member of the community.

*Meiklejohn, A. Twenty-five years in medicine. *Brit. M. J.* 1:930-932, 1953.

MASSACHUSETTS PHYSICIANS ART SOCIETY

16. "Tufts Jumbo"

Exhibited in First American Physicians Art Exhibit, 1938

Sculpture by

SIDNEY C. WIGGIN, M.D.

President, Massachusetts Physicians Art Society; Anesthesiologist, Boston City Hospital.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 39261

PRESENTATION OF CASE

First admission. A twenty-two-year-old stenographer was admitted to the hospital for re-evaluation of hypertension.

Six years previously the patient was thrown from a wagon when the horse ran away. She sustained injuries to the right arm and right side of the chest and was admitted to another hospital, where the diagnosis of ruptured right kidney was made, on the basis of gross hematuria and x-ray findings. The blood pressure on admission was 100 systolic, 80 diastolic. An intravenous pyelogram was normal except for an incomplete outline of the right kidney and marked deformity of the pelvis and major and minor calyxes. The patient was discharged after a month although hematuria was said to have persisted for about two months but to have gradually decreased in amount. The blood pressure at the time of discharge was not known.

Subsequently, she had urinalyses every six months and had no recurrence of hematuria until about four years later, when she began to complain of a low backache radiating around anteriorly. On several different occasions the urine was found to contain "a great deal of albumin and many red blood cells," and the blood pressure, although usually normal, rose to 150 systolic, 100 diastolic. There was no history of nausea or vomiting and no changes other than slight headache, which seemed to be associated with the periods of transient hypertension. She was again admitted to the other hospital for study. Significant findings on physical examination were slight resistance in the right upper abdomen, with much tenderness, especially on deep inspiration, and some tenderness posteriorly over the right kidney. The urine examination on two occasions revealed a specific gravity of 1.017, a few red cells and white cells and no albumin. The sedimentation rate was 4 mm. per minute, and the serum nonprotein nitrogen 29 mg. per 100 cc. Routine hematologic studies were negative. An intravenous pyelogram was normal except for slight blunting of the calyxes of the upper pole of the right kidney.

Three years and one year before admission ecchymoses of the arms and legs had appeared spontaneously or after minimal trauma and were said to have been associated with albumin and white blood cells in the urine. The purpura disappeared after treatment with pills of a type unknown to the patient. She was again admitted to the hospital, where a thrombocytopenia was said to have been discovered. The bleeding and clotting times were normal. The blood pressure on that admission was reported to have been 160 systolic, 120 diastolic. On subsequent visits to her physician she was found to have blood-pressure readings between 150 systolic, 110 diastolic, and 160 systolic, 120 diastolic. Since childhood she had been bothered by recurrent headaches, which had become increasingly frequent and severe in the year or so before admission. About nine months before admission, when she was referred to the Hypertensive Clinic of this hospital, she appeared healthy. Ophthalmologic examination was negative. There were fading ecchymotic areas over both forearms and upper and lower legs. The general examination was otherwise completely negative. The temperature, pulse and respirations were normal; the blood pressure was 160 systolic, 110 diastolic.

A catheterized specimen of urine was light yellow, had a specific gravity of 1.020 and gave a ++ test for albumin; the sediment contained 2 to 3 white cells per high-power field and a few bacteria but no red blood cells. Urine culture revealed rare colonies of *Staphylococcus albus*. Examination of the blood showed a hemoglobin of 13.4 gm. per 100 cc. and a white-cell count of 7300, with a normal differential. The nonprotein nitrogen was 15 mg. per 100 cc. A tourniquet test produced 32 petechiae in a 5-cm.-wide area on the right forearm. An electrocardiogram was normal. The patient refused admission to the hospital and was reluctant to have any further studies.

One month and two months later, when she returned to the Clinic, the blood pressure was found to be about the same as on the previous visit. An intravenous pyelogram was interpreted as being normal (Fig. 1), and a benzodioxane test was negative. During the following months before admission headaches were her chief complaint although she also experienced increasing fatigability in the afternoon.

Physical findings on admission were unchanged except that there was no purpura at this time. The temperature was 98.6°F., the pulse 100, and the respirations 20. The blood pressure was 192 systolic,

132 diastolic. A twenty-four-hour specimen contained less than 0.2 gm. of Esbach's protein. Urine culture was negative. The hemoglobin was 14.7 gm. per 100 cc. During the first several days in the hospital hourly readings of the blood pressure revealed that it ranged from 130 to 160 systolic and 92 to 120 diastolic. After the patient was given a trial dose of 0.13 mg. of protoveratrine intravenously the blood pressure dropped from 170 systolic, 116 diastolic, to 100 systolic, 58 diastolic. This was accompanied by few unpleasant effects, and therapeutic doses were begun. She was discharged a week later to the care of her physician and the Hypertension Clinic.

FIGURE 1. *Intravenous Pyelogram. Arrows point to the small right kidney.*

Final admission (one and a half years later). She was readmitted to the hospital because of progressive loss of vision during the previous two weeks.

Since the last admission she had headaches on the average of one out of every three days. These, which she graded as dull or mild to extremely severe, were generally frontal in location, were worse on the right side and lasted hours to a day. They were frequently present and most severe in the early morning. Often they began as a dull ache and gradually became severe and stabbing after a few hours. They were occasionally associated with nausea and photophobia. Some relief was afforded by Seconal, but none by ergotamine. Except for a period of about two months, during which the headaches were worse, the patient had received about 0.5 mg. of protoveratrine four times a day, with minimal unpleasant effects. The details of the blood-pressure response to this treatment were unknown, but it was estimated that there was 50 per cent improvement in the headaches. Six months before admission the blood pressure was recorded as 190 systolic, 130 diastolic. On that occasion fluoroscopic examination disclosed a vertically positioned but enlarged heart. On ophthalmologic study the borders of the optic disks were noted to be blurred. During the six months before admission there was increasing malaise, fatigability, nosebleeds and dyspnea, but the patient continued working until about two weeks before admission, when the appearance of ankle edema, dyspnea, anorexia and blurred vision forced her to bed. In the two days before admission she vomited repeatedly and her vision became worse.

Physical examination disclosed a woman who appeared chronically ill and who was pale and thin. There were ecchymoses of the lower legs and hemorrhagic crusts in both nostrils. There were obliteration of disk margins, tortuosity of retinal arterioles and a few scattered exudates and one linear hemorrhage in the right retina. The venous pressure was slightly increased, but no peripheral edema was noted. The heart was enlarged, the border of dullness extending 12 cm. to the left of the midsternal line in the fifth interspace. There was a soft, Grade 2, apical systolic murmur and an early diastolic blowing murmur along the left sternal border. Examination of the lungs and abdomen was negative, as was neurologic examination.

The temperature was 98.8°F., the pulse 112, and the respirations 24. The blood pressure was 240 systolic, 130 diastolic.

The urine had a specific gravity of 1.015 and gave a ++++ test for albumin; the sediment contained 0 to 2 white cells, 1 to 3 red cells and occasional granular casts per high-power field. Urine culture was negative. Examination of the blood showed a hemoglobin of 9 gm. per 100 cc. and a white-cell count of 11,300, with a normal differential. The platelets were estimated to be adequate. The nonprotein nitrogen was 94 mg. per 100 cc.; the sodium was 131 milliequiv., the potassium 4.8 milliequiv., the chloride 90 milliequiv., and the carbon dioxide 25 milliequiv. per liter. The blood pH was 7.43. An electrocardiogram indicated a regular rate of 100 per minute, a PR interval of 0.16 second and a QRS interval of 0.10 second; the R waves in Leads 2, 3, aVF and V_6 were high, the S waves in Lead V_2 diphasic, and the T waves in Lead V_6 low and those in Leads V_2 and V_4 slightly peaked. X-ray films of the chest showed an enlarged heart, a tortuous aorta, evidence of congestive heart failure at both lung bases and pleural fluid at the right base (Fig. 2).

On the second hospital day the patient complained of severe headache, vomited repeatedly and became very drowsy. A slight weakness of the right facial muscles was noted. The pulse was 112, and the blood pressure 270 systolic, 140 diastolic. She did

not improve on intravenous administration of protoveratrine. Twenty-four hours later a neurologist noted her to be unresponsive to verbal command, with a flaccid right hemiparesis and bilateral Babinski signs. A lumbar puncture disclosed an initial spinal-fluid pressure equivalent to 160 mm. of water; the spinal fluid contained no white cells and 3 red cells per cubic millimeter and a total protein of 104 mg. per 100 cc. Over the next several days the patient became comatose, the respirations irregular, and the temperature subnormal. The blood pressure fell to 120 systolic, 80 diastolic, and she became oliguric. The nonprotein nitrogen was 250 mg. per

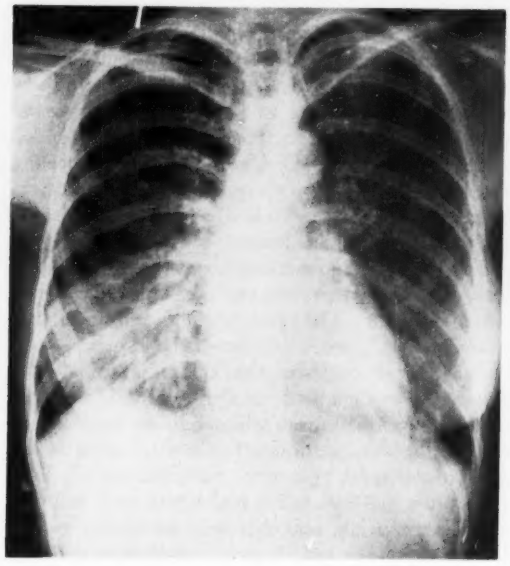

FIGURE 2. *Roentgenogram of the Chest.*

100 cc., and the serum sodium 121 milliequiv., the potassium 7.3 milliequiv., and the carbon dioxide 12.3 milliequiv. per liter.

On the ninth hospital day rales developed at both lung bases and respirations became shallower. She was found dead in bed on the next morning.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT WILKINS*: May I see the x-ray films?

DR. JOSEPH HANELIN: I do not have the original pyelograms made at the time of the injury; the set of pyelograms that I do have were made a little more than two years before death and show a small right kidney and a normal left kidney. The dye is excreted well on both sides and appears simultaneously in the two kidneys. I do not think there is any marked distortion of the calyceal pattern except slight blunting of the superior calyxes on the right side as described in the protocol (Fig. 1). About two years later, presumably at the time of the last admission, the kidneys are not too well shown; the patient has obviously lost intra-abdominal and subcutaneous fat in the interval. I suspect the kidneys are about the same in size. The chest films show a definitely enlarged heart, with a hypertensive configuration, a tortuous aorta, evidence of congestive heart failure at both lung bases and slight increase in pleural fluid at the right base (Fig. 2).

DR. WILKINS: There are many interesting points in the history of this young woman, who died of hypertension at the age of twenty-four. Indeed, one of the most important points is that she did die of her disease at such an early age. The course of the disease so far as time is concerned is important. At the age of sixteen she had suffered a traumatic rupture of the right kidney. At the age of twenty she had begun to complain of symptoms suggesting pyelonephritis and had had the first appearance of an intermittently elevated blood pressure associated with headaches. Within the next year or so the blood pressure became more elevated, particularly the diastolic pressure, but the eye grounds and the electrocardiogram remained normal. She then had the onset of a common symptom, in fact the most common symptom, of hypertension — namely, easy fatigability — and on admission to this hospital was found to have a diastolic pressure above 130. Although the blood pressure varied considerably in the hospital it never became normal except after the use of veratrum. She was discharged on this drug, but the actual course of the blood pressure over the next year and a half was unknown. Six months before death she stated that the headaches had become severe, were occasionally associated with nausea and photophobia and were relieved somewhat by veratrum. Within the last six months of her life the situation deteriorated rapidly, with progressive enlargement of the heart, retinopathy, malaise, fatigability, nosebleeds and shortness of breath followed by dependent edema, anorexia and blurred vision.

Physical examination confirmed the impression derived from the history that she was in the terminal stage of the disease, with marked elevation of the blood pressure, myocardial enlargement and progressive renal failure. She had a cerebral accident, became comatose and died.

There are some important unknown facts in the patient's history as given. Was there a family history of hypertensive cardiovascular disease? This is not an irrelevant point since we know that this patient had a history suggestive of renal hypertension. Platt,[1] in England, found that patients with supposed renal hypertension are not, as a rule, relieved of their hypertension by removal of a single diseased

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kidney, if they also have a strong or definite family history for essential hypertension.

DR. BENJAMIN CASTLEMAN: The patient's father died at the age of sixty; he had heart trouble and hypertension. Her mother was still living and well, and four siblings had no renal or vascular disease.

DR. WILKINS: I think Dr. Platt would accept that as "one plus" by his criteria — that is, one parent had hypertension; therefore, even if he had been quite certain that this woman's disease early had been confined to one side, he might have been somewhat less enthusiastic about removing the diseased kidney than if there had definitely been no hypertension in the family. In his review only 1 out of 11 patients with a definitely positive family history for hypertension was relieved by removal of the diseased kidney, whereas 8 of 12 cases with a negative family history for hypertension were relieved by removal of the unilaterally diseased kidney. Put another way, it would be uncommon indeed for essential hypertension of this severity to have appeared at this age unless there were a strong family history of the disease, and I personally think stronger than the indication of a father who died at the age of sixty. In the absence of a strongly positive history one naturally seeks another cause.

It is obvious that the physicians who took care of the patient thought of the possibility of pheochromocytoma, which cannot be absolutely ruled out even with a negative benzodioxane test. However, in my opinion, we have adequate explanations for the course without including this diagnosis, and so I prefer not to make it.

Another fact that I should like to know is the course of the renal failure. We have little information about the reserve of renal function before the terminal events. We do know that she had a normal nonprotein nitrogen within two years of her death. It would have been helpful to know what the renal-function capacity was as measured by some clearance technic, even by a fractional phenolsulfonephthalein test. This is important because although the terminal course suggested renal failure it is difficult to rule out the possibility that myocardial failure contributed significantly to the apparent renal failure. Granting that it did, I still think that the degree and progression of the terminal events suggest a malignant phase of hypertension and indicate that terminally the kidneys were severely damaged on both sides. The important point to be decided is whether the renal disease was primary or secondary.

Going back to the initial event in the history, I do not believe I can ignore the story of a ruptured right kidney with gross hematuria and a positive pyelogram. Could this have been the beginning of a Goldblatt hypertension? A split functional test of the separate kidneys before the malignant phase appeared might have helped in making this decision. Certainly, the only chance this patient ever had of being cured of her hypertension would have been if luckily a single diseased kidney had been responsible and had been removed before the terminal illness. Braasch,[2] of the Mayo Clinic, reports several cases due to ruptured kidney but it is interesting that he comments that the syndrome of Goldblatt hypertension more commonly occurs when a secondary pyelonephritis has been set up in the damaged kidney. It appears to me that in the case under discussion it was altogether likely that the patient had pyelonephritis on the right side at least, if not bilaterally.

Let me digress here a moment to mention a common occurrence in hospital-treated patients with urologic disturbances — namely, the frequent development of pyelitis and pyelonephritis. Dr. Arnold Relman, in our hospital, is convinced that this is due to catheterization. Catheterization, no matter how carefully it may be done, cannot be an aseptic technic. Infection is bound to be introduced into the genitourinary tract and possibly into the blood stream by this method. Undoubtedly, this young woman was catheterized frequently in the first hospital admission. Since she had a damaged and partially obstructed right kidney we know from the work of Mallory and his associates[3] that there was a good chance that pyelonephritis would develop on the damaged side. The patient had another attack of hematuria four years after the initial injury associated with low-back pain with a familiar renal-colic radiation. She then had renal tenderness, and the urine sediment contained white cells as well as red cells. Pyelograms continued to show blunting of the calyxes of the upper pole of the right kidney.

Later, the patient again had white cells and albumin in the urine, and this was associated with a history of ecchymoses. I have the feeling that the story of easy bruising and "thrombocytopenia" may be the "red herring" in this case. I am wondering if it could have been not a primary blood dyscrasia but a secondary purpura due to some medication such as sulfonamides, analgesics or sedatives for the relief of the pyelonephritis. Subsequent studies did not reveal any specific abnormalities of the blood. The tourniquet test mentioned later does not impress me in a patient as ill as this one was. The chief laboratory abnormalities were in the urine and consisted of albuminuria, white cells and bacteria, which on culture were *Staph. albus*. As already mentioned, she then went into an accelerated phase of the disease.

Did she have merely a unilateral renal disease and hypertension on the basis of a Goldblatt kidney? This is possible, but I think we should beware of attributing the whole course merely to the traumatic injury. As I have mentioned the evidence for pyelonephritis on the right was quite good, and there was also good clinical evidence that both kidneys were involved in some way. Whether or not the left kid-

ney was also involved by pyelonephritis, I can be certain that it became involved in the nephrosclerosis that must have developed before death. Even Goldblatt animals develop hypertensive vascular disease of the "normal" unclamped kidney, and when the clamped kidney is removed the blood pressure returns to normal in only half the animals. The others may be assumed to have a continuation of hypertension because of the vascular disease present in the remaining kidney. If a Goldblatt clamp is removed from a clamped kidney, half these animals in time will have a return of blood pressure to normal. The remaining hypertensive group can then be relieved of hypertension if the so-called normal kidney is removed but not if the previously clamped kidney is removed.[4] In this situation, presumably, the previously clamped kidney is actually the more normal, and the kidney that suffered from hypertension without the protection of the clamp the more diseased.

As I mentioned at the outset the terminal course of the hypertensive disease in this patient and her age suggest that this was a renal and not an essential hypertension. Perera and Haelig,[5] in New York, have described the characteristics of renal hypertension in a group of patients known to have had "renal" hypertension since they were all relieved of their hypertension after removal of a single diseased kidney. The patient under discussion resembled his group remarkably. The hypertensive disease in his group was characterized by a short, malignant course, high diastolic pressure, severe headache and retinopathy, including hemorrhages, exudates and papilledema. Infection was the commonest disease found in the kidneys of these patients.

Without doubt cardiac dilatation aggravated the terminal downhill course. The rapid cardiac enlargement and development of systolic and aortic diastolic murmurs indicate a rapid progression of the hypertensive disease to which the heart could not adjust. She became uremic and anemic and finally had a cerebral accident, probably a hemorrhage.

My diagnoses are malignant hypertension due to primary renal disease arising from old rupture of the right kidney, and probable pyelonephritis on the right, a question of bilateral pyelonephritis; terminal malignant nephrosclerosis; hypertensive heart disease, with dilatation of the left ventricle; and hypertensive cerebrovascular disease, with left-sided cerebral hemorrhage.

Dr. Alfred Kranes: I wonder why Dr. Wilkins did not consider more seriously the possibility of glomerulonephritis with a history of hematuria, elevated blood pressure and albuminuria during one phase of the illness.

Dr. Wilkins: Perhaps I should consider glomerulonephritis more seriously, but then I should be ignoring the fact that the first hematuria appeared after trauma. I think it would be more satisfactory to put all the eggs in one basket if I can. Obviously, there is no reason why the patient could not have had a traumatic lesion of the kidney followed by bilateral glomerulonephritis.

Dr. Walter Bauer: The patient may have had the two diseases: a congenital anomaly of the right kidney and Schönlein-Henoch purpura. The clinical record states that she had muscle and joint pains; however, objective articular signs are not mentioned — if they had been present the disease picture could be accounted for by Schönlein-Henoch purpura. Whether one can make this diagnosis on the basis of the late renal changes is the question.

Dr. Wilkins: I think that is a possibility; I had considered that she had some type of blood dyscrasia. It seems to me that a good deal of attention was paid to that possibility clinically and also at her initial injury to the fact that although she had hematuria she did not have excessive or massive bleeding elsewhere even though she did sustain injuries to the arm and chest. Although she may have had a blood dyscrasia, I believe that would be dragging in another diagnosis, and I prefer to take the straightforward course.

Dr. Bauer: Young people may have two diseases. We once saw a youngster of fourteen who had been kicked in the side during a football game and who soon thereafter entered the hospital because of hematuria and arthritis. We were unable to demonstrate renal injury as the cause of the hematuria. The finding of intracellular *Neisseria gonorrheae* in the prostatic smear and culture led us to conclude that the hematuria was a manifestation of an acute gonococcal urethritis and not of the injury.

Dr. Wilkins: That is a point well taken; both those possibilities could not be ruled out.

Dr. Robert S. Palmer: Before Dr. Wilkins discussed this case I thought it was absolutely typical of primary renal hypertension. After his discussion I am even more sure of it. The real question to me, in view of the suggestive pyelogram taken at the time the patient was injured, is this: Was this perinephritis due to injury (like experimental cellophane perinephritis), with superimposed infection first on the injured side and later on the other side? I should disregard the family history. The implication of my question is this. Would anybody here have had the courage, knowing what we do about renal hypertension, to remove a kidney from a young girl with a blood pressure no higher than 160 systolic, 100 diastolic, at the time when she was first seen? Do you think so, Dr. Colby?

Dr. Fletcher H. Colby: I do not know, Dr. Palmer. We have been conservative about this because we have believed that in so many cases of a rising blood pressure with some renal disease we might be depriving the patient of so many nephrons that might be quite useful. In this particular case, if

this was a Goldblatt kidney, it would have been important to have operated upon the patient when she had the ruptured kidney with definite pyelographic findings. I assume that in such patients the extravasated blood and urine around the renal pedicle form scar tissue and eventually cause enough compression to produce a Goldblatt kidney. If that is true, it is essential to operate early on these patients. At present, the tendency is to be much more conservative than we have been in the past.

Dr. Jacob Lerman: I saw the patient during the final admission, when she was very sick and losing ground rapidly. The Service was of the opinion, in agreement with Dr. Wilkins, that she had malignant hypertension due to unilateral renal disease resulting from the traumatized right kidney (Goldblatt kidney). It was thought that had we seen her a year or two previously we would have advised a retrograde pyelogram and if this had revealed an abnormality of the right kidney we would have urged nephrectomy.

Dr. Wilkins: I agree with Dr. Colby's conservative point of view; I think that all forms of so-called unilateral renal hypertension are so rare that immediate operation, except for definite urologic indications, is the wrong treatment on a percentage basis and that one had better be conservative and wait to see. I can only point out that we do know what happened eventually to this patient; we do not have to wait to see. For a while she was getting as much benefit from the therapy as that therapy might do on the average for 100 other hypertensive patients. I would certainly have been most reluctant to take out this patient's kidney if she had had bilateral kidney disease. I do not want anyone to get the impression that there is a good argument for taking out a kidney in every patient like this.

Dr. Palmer: The only ones that I know of that are really cured are young people around twenty. Did you mean exploration or removal in the early stage, Dr. Colby?

Dr. Colby: I meant exploration and drainage of the kidney — not its removal.

Clinical Diagnoses

Hypertensive cardiovascular disease.
Encephalopathy due to arterial hypertension.
Arteriolar nephrosclerosis, advanced stage.
Malignant nephrosclerosis with oliguria.

Dr. Robert Wilkins' Diagnoses

Malignant hypertension due to primary renal disease arising from old rupture of right kidney, and probable pyelonephritis on right.
?Bilateral pyelonephritis.
Terminal malignant nephrosclerosis.
Hypertensive heart disease, with dilated left ventricle.
Hypertensive cerebrovascular disease, with left cerebral hemorrhage.

Anatomical Diagnoses

(Malignant hypertension), with necrotizing arteriolitis, involving kidneys, severe, and adrenal capsule and pancreas.
Renal atrophy, with scar, right kidney, upper third, secondary to trauma.
(Fractured ribs and perirenal hematoma, eight years.)
(Uremia.)
Chronic pericarditis, uremic type.
Myocardial hypertrophy, hypertensive type.
Myocardial infarction, focal, subepicardial, acute.
Pulmonary congestion and edema.
Bronchopneumonia, focal.

Pathological Discussion

Dr. Castleman: At autopsy we found quite a disproportion between the size of the right and that of the left kidney. The left kidney weighed 160 gm. and showed many petechial hemorrhages and was quite red and slightly granular; its cortex was slightly decreased in size. The right kidney weighed only 65 gm.; its upper pole was markedly reduced in size, fibrotic and adherent to the diaphragm. The lower pole, which comprised a little more than half of this right kidney, was similar to the left kidney. All the renal arteries to the left kidney were perfectly normal and patent. There was an anomalous artery going separately to the upper pole of the right kidney; although it was very narrow it was patent as far as the hilus.

Microscopical examination showed that in this diseased upper pole all the tufts were completely scarred and atrophic; there were practically no tubules left. Many of the arteries were completely occluded — an appearance seen with disuse atrophy. In one section close to the hilus of the upper pole a large vessel demonstrated complete old thrombosis.

I assume that this was a result of hemorrhage in and around the kidney and that there was enough pressure, perhaps as Dr. Palmer said, in the nature of an experimental cellophane constriction, on the upper pole of the kidney to produce thrombosis in that artery and, combined with pressure atrophy of the upper pole of the kidney, to cause complete atrophy of the upper pole. The left kidney and the remainder of the right kidney showed the typical picture of malignant nephrosclerosis, severe arteritis and necrosis of the vessel walls, especially of afferent arterioles, with extension into the tuft. These areas of severe arteritis were scattered throughout both kidneys but not in the scarred upper pole. We also found an occasional vessel in the pancreas and in the capsule of the adrenal gland that revealed this necrotizing arteritis. The heart was enlarged, weighing about 400 gm., and contained a few foci of ischemic necrosis. The lungs demonstrated the type of hemorrhagic edema that we see quite often with uremia. The parathyroid glands showed definite secondary hyperplasia, indicating that the patient had had chronic renal impairment at least for a few years. The brain was quite interesting. I shall ask Dr. Adams to describe that.

Dr. Raymond D. Adams: The brain was heavy and weighed 1480 gm. The surfaces of the cerebral hemispheres were flattened, with narrowing of the sulci and squaring off of the convolutions, and a horizontal section disclosed swelling. The lateral ventricles were almost obliterated. There was no tentorial or cerebellar pressure cone. There was slight atherosclerosis of the basilar and carotid arteries. We have seen only a few microscopical sections thus far, and a necrotizing arteriolitis similar to that seen in the kidneys was found. Around the damaged arterioles there was necrosis of the tissue in small foci of 100 to 200 microns in diameter and petechial hemorrhages. Our impression at the moment is that there was a widespread necrotizing arteriolitis with brain edema and petechial hemorrhages — which appears to be the pathological equivalent of hypertensive encephalopathy. But, in addition, there were the two softenings, one in the left parieto-occipital region, measuring about 2 by 4 to 5 cm., and the other in the inferior part of the temporal lobe, for which we have no explanation as yet. Our other microscopical sections may enable us to determine the cause of these infarcts.

I had seen this patient clinically and believed, as Dr. Wilkins did, that the patient had several neurological conditions: first, hypertensive encephalopathy as shown by the headache, the disturbance of consciousness and the high spinal-fluid protein; and, secondly, a sizable vascular lesion in the left frontoparietal region, probably a small hemorrhage and thirdly, uremic encephalopathy. That clinical impression was only partly correct since no hemorrhage was found. The lateralizing neurologic signs were due to the infarcts in the left hemisphere.

Dr. Castleman: Whether this small area of atrophy or infarction in the right kidney was the precipitating factor in the hypertension I do not think we can finally decide. This could only have been determined if that kidney had been removed and the patient had been relieved of the hypertension. It is certainly suggestive that that was the mechanism. Some years ago Loomis,[6] working in Jean Oliver's laboratory, produced infarctions of the kidneys in rats. When she produced infarction of a part of a kidney, she noted that hypertensive changes were more likely to occur than if she produced infarction of the entire kidney; she believed that the collateral circulation in the partially infarcted kidney allowed the pressor substance to get into the blood. The case under discussion, in which there was infarction of about a third of the kidney, may have been the human counterpart. What is your opinion about that as the mechanism, Dr. Wilkins?

Dr. Wilkins: I should agree. Knowing the pathology, I am convinced that this was Goldblatt hypertension. If all the kidney is infarcted, Goldblatt hypertension does not result. There must be some viability, some living renal cells, which apparently are not getting the proper source of circulation, to produce this form of hypertension. That does not mean that the cells are totally ischemic but that they are not receiving the proper sort of circulation.

Dr. James H. Currens: I should like to raise the question whether the Goldblatt kidney is the right term to use here since the actual circulation to the pedicle was all right; only a small portion of the circulation of the kidney was impaired. I did write to Dr. K. G. Kohlstaedt, who was active in the work with cellophane and silk in the production of experimental renal hypertension,[7] about this case; his comment was as follows:

During our studies of production of hypertension by wrapping the kidney in cellophane we observed on several occasions that it was necessary to include only a part of the kidney in the scar of perinephritis to produce a rise in blood pressure. I remember one animal in which the cellophane bag had slipped so that only a corner of the kidney was included, yet this dog developed a marked hypertension. We also used silk bags prepared so that the pedicle of the kidney was free, and hypertension occurred. In other animals only the string and silk was left about the pedicle, and hypertension did not occur. This was done to prove that the cellophane method did not cause hypertension because of the constriction of the renal artery by the string tied about the base of the kidney.

This, of course, may be a similar phenomenon, but the technic is different from the Goldblatt technic and it was Dr. Kohlstaedt's notion that lack of pulsability of the kidney was the important feature in experimental renal hypertension produced with cellophane.

I saw this patient five months before death and noted the early blurring of the optic-disk margins but, of course, did not realize that her condition would deteriorate so rapidly. She was advised at that time to return to the hospital for further observation and declined to do so.

DR. WILKINS: I think that Dr. Goldblatt would insist that this was Goldblatt hypertension.

DR. BAUER: If you had seen this woman two years before her death, would you have removed the right kidney?

DR. WILKINS: If I saw a patient like this again —I am a little smarter than I was before I discussed this case — who had clear-cut evidence of injury with hematuria and hypertension, when the hypertension reached a considerable degree — a diastolic pressure of 130 or higher (which George Perera thinks is characteristic of his group of this sort) — and before it became malignant, I should strongly recommend exploration; if this sort of condition were found, I do not think there would be any question about the operative procedure.

DR. BAUER: It is of interest that the patient's physician, on referring her to our hospital, called attention to the likelihood of renal injury and inquired about the advisability of nephrectomy. After her first hospital entry he rightly asked whether this therapeutic possibility had been entertained and whether our diagnostic studies had ruled it out. If the doctor is here I wish he would review the case.

DR. WILLIAM CRANDALL: This patient had been studied in another clinic before I saw her; she had had numerous petechiae, and was found to have diminished platelets. The petechiae disappeared, and the number of platelets became normal. That is all we know about that episode. When she came to me, and I took her blood pressure, I knew that I could not treat her. I knew that diagnostic studies at my hospital would not be complete and would have to be repeated and supplemented at a larger institution.

REFERENCES

1. Platt, R. Heredity in hypertension. *Quart. J. Med.* **16**:111-133, 1947.
2. Braasch, W. F., and Strom, G. W. Renal trauma and its relation to hypertension. *J. Urol.* **50**:543-549, 1943.
3. Mallory, G. K., Crane, A. R., and Edwards, J. E. Pathology of acute and of healed experimental pyelonephritis. *Arch. Path.* **30**: 330-347, 1940.
4. Floyer, M. A. Effect of nephrectomy and adrenalectomy upon blood pressure in hypertensive and normotensive rats. *Clin. Sc.* **10**:405-421, 1951.
5. Perera, G. A., and Haejig, A. W. Clinical characteristics of hypertension associated with unilateral renal disease. *Tr. A. Am. Physicians* **65**:134-158, 1952.
6. Loomis, D. Hypertension and necrotizing arteritis in rat following renal infarction. *Arch. Path.* **41**:231-268, 1946.
7. Page, I. *Experimental Renal Hypertension.* 72 pp. Springfield: Charles C Thomas, 1948.

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UNIVERSITIES AND THEIR FACULTIES

THE current investigations of loyalty initiated by Congress have tended to confuse in the minds of teachers themselves as well as of the public the rights and the obligations of universities and their faculties. A statement of these rights and responsibilities was consequently adopted and published this spring by the Association of American Universities, composed of an imposing list of 37 of the country's leading institutions of higher education.

This confused matter is especially important in the United States because of the prevailing thirst for knowledge and the unusual opportunities there are for gratifying it. Elsewhere there may be an equal thirst but less opportunity for its indulgence. The matter is especially important in this country because of the tendency here to go to extremes; because of a political immaturity that demands quick and sometimes violent action lest a cooling off and the exercise of more sober judgment should diminish the apparent need for action.

The pattern established by American universities is generally creditable. In them the "scientific, technological, medical and surgical advances of our time were born"; in them these disciplines have been nurtured and have developed. Their obligation is to search out and to reveal the truth wherever it may be found and however unpleasant it may seem. There can be no retrograde reasoning from a prefabricated conclusion back through a spurious line of investigation, as has been known to be the case with the politically controlled science of the soviets.

The modern American university is an association of independently thinking scholars whose main requirements are that they must be capable in the pursuit of knowledge and in the communication of it to others. It appears also to be a reasonable requirement that they must be loyal to the moral code, to the country and to its form of government. They must meet the obligations of citizenship if they are to enjoy its privileges.

Academic freedom, then, may be interpreted as the right to investigate, criticize and present ideas "in an atmosphere of freedom and mutual confidence." It does not relieve any teachers of the necessity of living within the law, but neither should it impose on them restrictions or penalties beyond those exacted of other citizens. There should be no regulation that requires or any threat that impels the scholar "to stand silent when he ought to speak, particularly in the field of his competence."

The greater the privilege, however, the greater the responsibility. The university guarantees standards of intellectual quality, but as it implies endorsement of its members' capability and integrity, it requires also of every scholar that he should maintain such a reputation. The candor and integrity that the professor owes his colleagues are obligations "precluding any kind of clandestine or conspiratorial activities." And the university itself, operating with special rights and exemptions,

owes to the state the duty of co-operation in upholding the law.

Freedom, independent nations are learning, is not a right but a privilege, and "'academic freedom' is not a shield for those who break the law." According to the statement of the Association:

> We condemn Russian Communism as we condemn every form of totalitarianism. We share the profound concern of the American people at the existence of an international conspiracy whose goal is the destruction of our cherished institutions. The police state would be the death of our universities, as of our government. Three of its principles in particular are abhorrent to us: the fomenting of world-wide revolution as a step to seizing power; the use of falsehood and deceit as normal means of persuasion; thought control — the dictation of doctrines which must be accepted and taught by all party members. Under these principles, no scholar could adequately disseminate knowledge or pursue investigation in the effort to make further progress toward truth.

At the same time the dangers of a reactionary fascism — another type of totalitarianism — are to be avoided at nearly any cost. The university teacher certainly should be entitled to no special privileges under the law; neither should he — or any other citizen — be subject to special discriminatory persecution.

FURTHER PHARMACEUTICAL FACTS

A LETTER published elsewhere in this issue of the *Journal* from the postmaster in charge of public relations in the Boston district calls attention to a situation that is, in a way, complementary to the one mentioned in last week's editorial, "Pharmaceutical Fact and Fancy." This situation is the thoughtless disposal of drug samples in public waste receptacles by physicians. Both communications relate to the use or misuse of active and consequently potentially dangerous drugs. The editorial refers to the occasional lack of discrimination in their employment; the letter implies a lack of care in their disposal that seems hardly attributable to physicians.

The physician is at all times a guardian of the public health; it is an obligation he has assumed with the acceptance of his degree, and he cannot escape from his responsibility even if he would. Obviously, the placing of completely unnecessary hazards in the public way represents a form of carelessness that needs to be brought to the individual physician's attention but once.

Any discussion of the subject raises a more fundamental question in relation to the whole pernicious custom of the widespread distribution of unsolicited samples by the manufacturers of pharmaceutical products. These concerns must be well aware that the majority of their elaborately packaged offerings go into waste receptacles, public or private, and that the cost of this extravagance is borne by the legitimate consumer. A relatively small percentage of these samples is collected by charitable agencies and sent to needy institutions at home or abroad.

Let the suggestion be made here that the manufacturers will serve a triple purpose by giving directly to charity each year, economically packed for shipment, the same proportion of their products that is now distributed blindly, and send samples to physicians only on request. They will thus contribute usefully where the need may be greatest, effect a saving that might logically reduce the price of the product to the patient, and help to keep potentially dangerous drugs out of the wastebaskets of the nation.

REMEMBERING THE ALAMO

THE history of Texas is part of the record of American independence. First visited by the Spanish when Cabeza de Vaca landed on its shores in 1528 — although not permanently settled until 1682 — what was later to become the Lone Star State remained part of Mexico for a century and a half. Then came its war of independence, with the Alamo as a rallying cry, and the establishment of the republic in 1836 under the presidency of Sam Houston.

In 1845 Texas accepted statehood, and only eight years later — a century ago as time flies — the Texas Medical Association was founded. This event took place appropriately in the Methodist Church in Austin on January 17, 1853, when 35 physicians from various parts of the youthful state met for the purpose. The present membership of the Association is over 6500 — approximately that of the Massachusetts Medical Society — but the auxiliary, of 4500 wife power, is more than double that which the Bay State can yet boast, as

well as being some thirty years older (as an organization).

The Texas Medical Association met again in November, 1853, and then, for reasons unknown but possibly related to the vast geography of the region, suspended operations until 1869. A cohesive factor in the present century has been the outstanding *Texas State Journal of Medicine*, now in its forty-ninth volume, the May number of which has been devoted to the centennial.

The *New England Journal of Medicine* salutes the new centenarian among medical societies — its membership, its auxiliary and its journal.

The New York Medical Gazette states that 29 suicides, 5 murders and 209 cases of insanity are directly traceable to spiritual manifestations as the cause.

Boston M. & S. J. *June 29, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

BILL — José Penteado Bill, M.D., of Boston and Wayland, died on June 8. He was in his seventieth year.

Dr. Bill received his degree from Harvard Medical School in 1916. He was assistant professor of public health and preventive medicine at Boston University School of Medicine. He was a fellow of the American Medical Association and a member of the American Public Health Association.

He is survived by his widow and two daughters.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

LABORATORIES APPROVED FOR DIAGNOSTIC SEROLOGIC TESTS FOR SYPHILIS

For convenient reference, the forty-three laboratories approved for standard tests for syphilis to August, 1954, are listed below. Legally, only these laboratories and the Wassermann Laboratory of the Department of Public Health may perform the *premarital* and *prenatal* blood tests required by law.

The Wassermann Laboratory, at 281 South Street, Jamaica Plain, is the only laboratory in Massachusetts whose reports for premarital purposes are recognized in other states.

LOCATION	LABORATORY
Attleboro	Sturdy Memorial Hospital
Ayer	Community Memorial Hospital
Boston	Boston Dispensary
	Boston Health Department
	Commonwealth Clinical Laboratory
	Leary Laboratory
	Massachusetts General Hospital
	Massachusetts Memorial Hospitals, Genito-Infectious Disease Clinic
Brockton	Brockton Health Department
Brookline	Sias Laboratories
Cambridge	Mount Auburn Hospital
Clinton	Clinton Hospital
Fall River	St. Anne's Hospital
	Union Hospital
Fitchburg	Burbank Hospital
Gardner	Henry Heywood Memorial Hospital
Great Barrington	Fairview Hospital
Greenfield	Franklin County Public Hospital
Holyoke	Holyoke Hospital
	Providence Hospital
Lawrence	Lawrence General Hospital
Lowell	Lowell General Hospital
Montague	Farren Memorial Hospital
New Bedford	Burt Clinical Laboratory
	St. Luke's Hospital
Newton	Newton–Wellesley Hospital
North Adams	North Adams Hospital
Norwood	Norwood Clinical Laboratory
Pittsfield	Hillcrest Hospital
	Pittsfield General Hospital
	St. Luke's Hospital
Quincy	Quincy City Hospital
Salem	Salem Hospital
Springfield	Mercy Hospital
	Springfield Hospital
Stoneham	New England Sanitarium and Hospital
Taunton	Morton Hospital
Tewksbury	Tewksbury State Infirmary
Waltham	Waltham Hospital
Worcester	Worcester Health Department Laboratory
	St. Vincent Hospital
	Worcester City Hospital
	Worcester Hahnemann Hospital

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The July and August schedule of the Consultation Clinics for Crippled Children in Massachusetts is as follows:

ORTHOPEDIC	DATE	CLINIC CONSULTANT
Salem	July 6	Paul W. Hugenberger, M.D.
Gardner	July 7	Carter R. Rowe, M.D.
Haverhill	July 8	William T. Green, M.D.
Brockton	July 9	George W. Van Gorder, M.D.
Lynn*	July 13	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Pittsfield	July 15	Edward J. Coughlin, Jr., M.D.
Worcester	July 17	John W. O'Meara, M.D.
Springfield	July 21	James D. Fisher, M.D.
Hyannis	July 23	Paul L. Norton, M.D.
Greenfield	August 6	Charles L. Sturdevant, M.D.
Lowell	August 14	Albert H. Brewster, M.D.
Fall River	August 24	David S. Grice, M.D.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

Rheumatic-Fever Clinic	Dates
Fitchburg	July 1, 8, 15, 22, 29
North Reading	July 7, 14, 21, 28

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the District Health Officer to make appointments. Patients are seen by appointment only.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MAY, 1953

Disease	May 1953	May 1952	Seven-Year Median
Chancroid	4	3	3
Chicken pox	2579	1602	1865
Diphtheria	3	5	14
Dog bite	1411	1388	1421
Dysentery, bacillary	8	5	5
Encephalitis, infectious	4	6	3
German measles	1577	3920	744
Gonorrhea	177	162	218
Granuloma inguinale	0	0	0
Hepatitis, infectious	101	25	4†
Lymphogranuloma venereum	0	1	0
Malaria	1	4	4
Measles	456	5842	2385
Meningitis, meningococcal	14	7	5
Meningitis, Pfeiffer bacillus	5	6	5
Meningitis, pneumococcal	2	5	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	1	1
Meningitis, undetermined	5	2	4
Mumps	1661	721	1057
Poliomyelitis	8	4	1
Salmonellosis	12	9	10
Scarlet fever	469*	378	649
Syphilis	139	194	194
Trichinosis	5	1	1
Tuberculosis, pulmonary	216	203	207
Tuberculosis, other forms	7	17	17
Typhoid fever	3	2	2
Undulant fever	0	2	4
Whooping cough	130	97	389

*Includes streptococcal sore throat.

†Four-year median.

Comment

The diseases below the seven-year median were diphtheria, measles, scarlet fever and whooping cough.

Three cases of diphtheria were reported in May. This brings the total number of cases for the twelve months since June 1, 1952, to only 14, a remarkably low figure.

The 456 cases of measles reported in May make this the lowest figure by far for this month in the history of this state, the seventh month in succession to make a new low record. The epidemic last year left few children to catch measles.

The diseases above the seven-year median included chicken pox, German measles, meningococcal meningitis, mumps and poliomyelitis.

Although the incidence of chicken pox was high, for the first time in six months a new high record was not established.

Meningococcal meningitis was at the highest level since 1945.

Eight cases of poliomyelitis were reported in May, the highest for the month since 1949.

Geographical Distribution of Certain Diseases

The following diseases were reported from the communities named:

Anthrax: Peabody, 1.

Diphtheria: Boston, 1; Chelsea, 1; Sudbury, 1; total, 3.

Dysentery, bacillary: Boston, 3; Leominster, 1; Newton, 1; Waltham, 3; total, 8.

Encephalitis, infectious: Lynn, 1; Newton, 1; North Adams, 1; Springfield, 1; total, 4.

Hepatitis, infectious: Attleboro, 1; Auburn, 1; Belchertown, 13; Boston, 11; Boylston, 2; Brookline, 2; Cambridge, 1; Chicopee, 1; Dover, 1; Falmouth, 1; Fitchburg, 1; Fort Devens, 1; Freetown, 1; Holyoke, 3; Lexington, 6; Lowell, 2; Millbury, 7; Needham, 1; Newton, 1; North Adams, 1; Northboro, 2; Oxford, 2; Plymouth, 1; Quincy, 2; Sharon, 1; Shrewsbury, 1; Somerset, 1; Somerville, 1; Springfield, 4; Westboro, 1; Winthrop, 1; Worcester, 26; total, 101.

Malaria: Fort Devens, 1; total, 1.

Meningitis, meningococcal: Boston, 4; Brockton, 1; Douglas, 1; Foxboro, 1; Haverhill, 1; New Bedford, 1; Pittsfield, 1; Plymouth, 1; Salem, 1; Springfield, 1; Worcester, 1; total, 14.

Meningitis, Pfeiffer bacillus: Beverly, 1; Boston, 1; Holyoke, 1; Needham, 1; Quincy, 1; total, 5.

Meningitis, pneumococcal: Abington, 1; Waltham, 1; total, 2.

Meningitis, mumps: Groton, 1; Holliston, 1; total, 2.

Meningitis, undetermined: Amesbury, 1; Cambridge, 1; Charlton, 1; Douglas, 1; Winthrop, 1; total, 5.

Poliomyelitis: Boston, 1; Deerfield, 1; Haverhill, 2; Lynn, 1; Pittsfield, 1; Tyringham, 1; Waltham, 1; total, 8.

Salmonellosis: Arlington, 1; Boston, 1; Chicopee, 1; Ludlow, 1; Malden, 1; Medford, 2; Revere, 1; Somerville, 1; Westboro, 1; Westfield, 1; Whitman, 1; total, 12.

Trichinosis: Cambridge, 2; Milford, 1; New Bedford, 1; Williamstown, 1; total, 5.

Typhoid fever: Clinton, 1; Weymouth, 1; Worcester, 1; total, 3.

CORRESPONDENCE

NORFOLK DISTRICT IN MEDICAL EDUCATION

To the Editor: For your information an informal report is submitted of work done in the Norfolk District Medical Society during the current year in financial support of medical education.

An American Medical Education Foundation Committee was organized under the chairmanship of the undersigned, consisting of Drs. James M. Faulkner, Roy J. Heffernan and George P. Sturgis, representing Boston University, Tufts and Harvard respectively, and Dr. Irving J. Shalett, representing all other schools. Dr. Shalett was aided considerably by fifteen other members of the Society, each of whom undertook to canvass the alumni of his own school.

As a result it was found that up to April 28, 1953, 274 members of Norfolk, or 25 per cent of the membership, had made some sort of contribution either to their own school funds or to the American Medical Education Foundation since July 1, 1952. All members of the Society were approached, by personal contact, telephone or letter. A breakdown is submitted herewith:

School	Graduates in Norfolk District	No. of Contributors	Percentage
University of Virginia	5	5	100
New York University	9	7	78
Columbia University	11	7	63
University of Pennsylvania	18	10	56
Harvard	273	142	52
Johns Hopkins University	12	6	50
Yale	10	5	50
Boston University	106	30	28
Jefferson	4	1	25
Middlesex	98	17	17
University of Vermont	9	1	11
Tufts	321	35	11
Canadian schools	20	1	5
Other schools in United States	146	6	4
Foreign schools	49	1	2
Totals	1091	274	
Average			25

It is impossible to know whether this is a good, bad or indifferent record. Doubtless all contributors have not been listed, but the figures, although not necessarily accurate, are at least an indication. It will be interesting to learn how other district societies have fared in this regard.

Thomas R. Goethals, M.D.

MORE ON PLANTAR WARTS

To the Editor: I have recently been much amused by the reports of new discoveries about plantar warts, your editorial, and now the, to me, much more readable letter from Dr. Grund. It seems remarkable that in all my years of practice, which I am certain included many a plantar wart, I never was scared more than half to death by these lesions. To me, over the years, certainly thirty-five, a plantar wart was just another wart. Of course one would not expect a wart in such a location to be as little discomfort to the wearer or as amenable to quick and fairly

painless extirpation as one on most other locations but with ordinary care and diligence, with simple injection treatment, which certainly should include an efficient local anesthetic as a first step, and later by injection and fulguration, I do not recall a case in which any serious difficulty was encountered — nothing beyond the occasional need for retreatment after recurrence. As for the newness of novocain injection I certainly must have been using some such method as early as 1922.

R. H. GILPATRICK, M.D.

Cocoa, Florida

DISPOSAL OF DRUG SAMPLES

To the Editor: Among the many box holders in our various post offices are a number of doctors of all types who are constantly the recipients of much advertising matter and samples of pharmaceutical products. After removing mail from their boxes, some of these doctors stop at our lobby desk and run through their mails, after which what is not wanted is deposited in our wastebasket.

Frequently, the discarded mail includes samples of tablets that, if taken by a child or other person without prescription, might have dire results. In some cases we have eliminated this by cautioning the doctors individually. You will realize that any matter placed in a public disposal is subject to rummaging by children or others in search of something that might prove of interest or value.

So long as the service windows are open efforts are made to stop those seen rummaging through these wastebaskets. Children, however, have taken matter from the baskets and in some cases disposed of it on the front lawn of the post office.

We are particularly concerned with the samples of medicine because of the attractive cellophane packaging of samples of tablets. It is feared that some child may find a package of candy-coated tablets and, thinking they are candy, devour them with delight only to turn up seriously ill or worse.

Only recently an empty glass container enclosed in a package, marked "Digitora," was found on one of our post-office lawns. Both the package and the bottle were completely unsoiled, but the contents were missing. Several other samples of medicinal articles have been reported in the past month.

We believe, as you do, that "An ounce of prevention is worth a pound of cure." I think you will agree that it would be a serious reflection on the medical profession if, through the inconsiderate action of some physician, a child became seriously ill or died. Perhaps you are in the best position to spread a word of caution to the members of the profession in all its branches. I am sure that your editorial staff will know how to handle such a situation, and I should be pleased to receive any comments they have in this respect.

J. P. W. FINN
Postmaster

United States Post Office
Boston

RESTORATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held May 28, 1953, it was voted to restore the registration of Dr. Nathan W. Coleman, of Milton, Massachusetts.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Le derivazioni unipolari nell'elettrocardiografia clinica. By Giovanni Gigli, assistant, Instituto di Patologia Medica dell' Universita di Pisa. With a preface by Prof. G. Monasterio. 8°, paper, 260 pp., with 148 illustrations. Pisa: Omnia Medica, 1952. L. 2.000.

This monograph is written from the clinical point of view. The material is well arranged and is divided into six sections. The first two, which consider electrocardiography in general and the unipolar electrocardiogram, are followed by discussions on the organic and functional alterations of the myocardium and on the arrhythmias. The final chapters are devoted to extracardial conditions, diagnosis and the relative value of the electrocardiogram in general and the unipolar lead. Bibliographies are appended to the chapters; the publishing is good.

Osteosklerose und Knochenmarkfibrose. By Rudolph Stodmeister, Dr. med. Dr. phil., professor of internal medicine, Universität Heidelberg, and chief physician, Internal Division, Städtischen Krankenhauses Pforzheim; and Stefan Sandkühler, Dr. med., assistant, Ludolph-Krehl-Klinik (Medizin. Univ., Klinik), Heidelberg. With the assistance (on roentgenologic aspects) of Albert Laur, Dr. med., assistant, Division of Roentgenology, Ludolph-Krehl-Klinik (Medizin. Univ.-Klinik), Heidelberg. 8°, paper, 135 pp., with 29 illustrations. Stuttgart: Georg Thieme, 1953. DM 28.50. (Distributed by Grune and Stratton, New York.)

In this monograph the authors discuss osteosclerosis and fibrosis of the bone marrow. Case histories are included throughout the text, and the literature is evaluated. There is a bibliography of 16 pages and indexes of authors and subjects. The publishing is excellent. The small volume should be in all collections on the subject.

Morbus Alzheimer and Morbus Pick: A genetic, clinical and pathoanatomical study. By Torsten Sjögren, Hakon Sjögren and Ake G. H. Lindgren. 8°, paper, 152 pp., with illustrations. Copenhagen: Ejnar Munksgaard, 1952. 25 Swedish Crowns. (*Acta Psychiatrica et Neurologica Scandinavica*, Supplement No. 82.)

The 1952 Year Book of Radiology (June 1951–June 1952). Radiologic Diagnosis. Edited by Fred Jenner Hodges, M.D., professor of roentgenology and chairman, Department of Roentgenology, University of Michigan Medical School; and John Floyd Holt, M.D., associate professor of roentgenology, University of Michigan Medical School. *Radiation Therapy.* Edited by Harold W. Jacox, M.D., professor of radiology, Columbia University College of Physicians and Surgeons, and chief, Radiation Therapy Division, Radiologic Service, Presbyterian Hospital, New York City; and Vincent P. Collins, M.D., professor of radiology and chairman, Department of Radiology, Baylor University College of Medicine, and radiologist-in-chief, Jefferson Davis Hospital, Houston, Texas. 8°, cloth, 416 pp., with 387 illustrations. Chicago: Year Book Publishers, Incorporated, 1952. $7.50.

This volume of a standard reference work, first published sixteen years ago, maintains the excellence of its publication. The text consists of excerpts from outstanding articles in their particular fields. There are good indexes of subjects and authors. The volume should be in all collections on the subject.

Opiate Addiction: Psychological and neurophysiological aspects in relation to clinical problems. By Abraham Wikler, M.D., experimental neuropsychiatrist, National Institute of Mental Health, Addiction Research Center, United States Public Health Service Hospital, Lexington, Kentucky. 8°, cloth, 72 pp. Springfield, Illinois: Charles C Thomas, 1952. $3.00. (Publication No. 161, *American Lecture Series.*)

In this small monograph Dr. Wikler reviews the current literature on two aspects of opiate addiction. He especially discusses the mechanism of action of morphine in single doses in relation to the psychologic and neurophysiologic aspects and tolerance and the abstinence syndrome. There is a bibliography of 99 references and an index of subjects.

Health Education Yearbook 1952. Compiled by Oliver E. Byrd, Ed.D., M.D., professor of health education and director, Depart-

ment of Hygiene, School of Education, Stanford University. With a foreword by Gloyd Gage Wetherill, M.A., M.D., director of health education, San Diego City Schools. 8°, cloth, 232 pp. Stanford, California: Stanford University Press, 1952. $3.50.

This new volume of a well known reference series covers the whole field of health and comprises 273 abstracts from worthwhile articles. There is a bibliography of 273 articles and an index of authors and subjects. The volume is recommended to all medical libraries and to all persons interested in public health.

Unipolar Lead Electrocardiography and Vectorcardiography: Including the standard leads, the aV and V leads, the cardiac arrhythmias and the principles of vectorcardiography. By Emanual Goldberger, M.D., associate attending physician, Montefiore Hospital, cardiologist and attending physician, Lincoln Hospital, New York City, and consulting cardiologist, Saint Joseph's Hospital, Yonkers, New York. Third edition, thoroughly revised. 8°, cloth, 601 pp., with 312 illustrations. Philadelphia: Lea and Febiger, 1935. $10.00.

In this new edition Dr. Goldberger has made numerous changes, including the rewriting of the section of the functional changes in the R and ST segment and T wave. Much new material has been added throughout the text, especially on the electrocardiogram in infants and in congenital heart disease. The chapter on angina pectoris, myocardial anoxia and subendocardial infarction has been rewritten and enlarged. The bibliography has been brought up to date, and there are 439 references. There is a good index, and the book is well published.

The White Plague: Tuberculosis, man and society. By René Dubos, M.D., and Jean Dubos, Sc.D. 8°, cloth, 277 pp., with 13 illustrations. Boston: Little, Brown and Company, 1952. $4.00.

The authors have written a semipopular story of tuberculosis, especially of the nineteenth century. The text is divided into four parts: the disease in the nineteenth century; the causes; cure and prevention; and tuberculosis and society. The last part discusses the evolution of epidemics, tuberculosis and industrial civilization and social technology. There are 29 pages of bibliography and notes and a good index. The publishing is excellent. The book should be in all medical and public libraries.

Essentials of Infant Feeding for Physicians: A practical text for rapid reference. By Herman Frederick Meyer, M.D., assistant professor, Department of Pediatrics, Northwestern University Medical School, and associate attending physician, Children's Memorial Hospital, Chicago. 8°, cloth, 252 pp., with 12 illustrations and 40 tables. Springfield, Illinois: Charles C Thomas, 1952. $6.75.

Dr. Meyer has written a manual for physicians on infant feeding, in which the direct approach is toward the application of the practical principles of chemistry and physiology to infant nutrition. A short history of the subject precedes the text proper. The book begins with breast feeding, and the following chapters discuss the physiology of feeding, artificial feeding, mixed feeds, mixtures, proprietary foods, solid food supplements and vitamin supplements. There are also short chapters on psychologic feeding problems and "self-demand" feeding and "rooming-in." An appendix is devoted to tables and supplementary data, including a list of proprietary infant food products. An interesting frontispiece presents an armamentarium of such products. There is a bibliography and a good index. This concise book should prove valuable to the practicing physician. It should also be of value to medical libraries as a reference source.

Protein and Enzymes. By Kaj Ulrik Linderstrom-Lang. 8°, paper, 115 pp., with 65 illustrations and 15 tables. Stanford, California: Stanford University Press, 1952. $3.00. (*Lane Medical Lectures. Stanford University Publications, University Series, Medical Sciences*, Vol. 6.)

These five lectures describe in detail the research done in the last fifteen years in the dissection of cells and tissues for the purpose of investigating individual enzymes. The first two lectures discuss micromethods and their application to the problems of the actual distribution of enzymes in tissues and cells. The third and fourth lectures are devoted to the breakdown of proteins by enzymes, and the discovery of a new protein, "plank-albumin," which appeared after the breakdown of ovalbumin by a bacterial enzyme. The last lecture deals with the reversal of the breakdown process, or the general problem of protein synthesis in biologic material, in the cells of living organisms.

Therapeutic Meal Plans: A new diet manual. Prepared by the Department of Dietetics and Nutrition, University of Kansas School of Medicine. Edited by Virginia Toews, Berdena Rosenow and Ruth Gordon, dietitians. 8°, cloth, 111 pp., with 23 tables. Lawrence: University of Kansas Press, 1952. $3.00.

This new diet manual has been prepared for the use of the staff of the Medical Center of the University of Kansas. An adequate diet for every condition is the aim of the meal plans, and the normal diet is used as the basis for every diet. Simplified terminology has been employed, the title describing the diet and not the disease. In the calculation of the approximate vitamin and mineral composition for each meal plan, the minimum listings of *necessary foods* were used. For physicians a separate booklet of diets for medical and surgical conditions is provided in a pocket at the back of the manual. There are special chapters on pregnancy and lactation, infant and child feeding and test diets.

Radiologic Diagnosis of the Lower Urinary Tract. By Donald E. Beard, M.D., assistant in urology, Emory University School of Medicine, and visiting urologist, Grady Memorial Hospital, Atlanta; William E. Goodyear, M.D., assistant in urology, Emory University School of Medicine, and visiting urologist, Grady Memorial Hospital, Atlanta; and H. Stephen Weens, M.D., professor of radiology and chairman, Department of Radiology, Emory University School of Medicine, and radiologist, Grady Memorial Hospital and Emory University Hospital, Atlanta. 8°, cloth, 143 pp., with 279 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $6.50.

This small atlas is intended primarily for the radiologist and urologist, but should prove useful in part to the practicing physician and to the medical student. The main part of the text deals with the urethra and the bladder. There is also a chapter on urethrography and cystography in children. There is a bibliography of 4 pages and a good index. The illustrations are excellent. The book should be in radiologic and urologic collections.

NOTICES

ANNOUNCEMENT

Dr. Ezra Jacobs announces the removal of his office from 976 Blue Hill Avenue to 347 Geneva Avenue, Dorchester, where he will continue in the practice of eye, ear, nose and throat.

AMERICAN ACADEMY OF PEDIATRICS

The twenty-second annual meeting of the American Academy of Pediatrics will be held in Miami, Florida, with seminars at the McAllister Hotel on October 4 and 5 and general sessions at the Municipal Auditorium, October 6–9. In addition the program will include round-table discussions, scientific and commercial exhibits, a banquet, committee luncheons and entertainment.

Further information regarding program and registration may be obtained from the Executive Offices of the Academy, 610 Church Street, Evanston, Illinois.

AMERICAN ASSOCIATION OF BLOOD BANKS

The sixth annual meeting of the American Association of Blood Banks will be held in Chicago, Illinois, October 17–20, with headquarters at the LaSalle Hotel. The program will include scientific meeting, exhibits, a refresher course for technologists and round-table and panel discussions.

SOCIETY MEETINGS AND CONFERENCES

JULY 8 and 9. Seventh Annual Rocky Mountain Cancer Conference. Page 644, issue of April 9.

AUGUST 18–21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Page 707, issue of April 16.

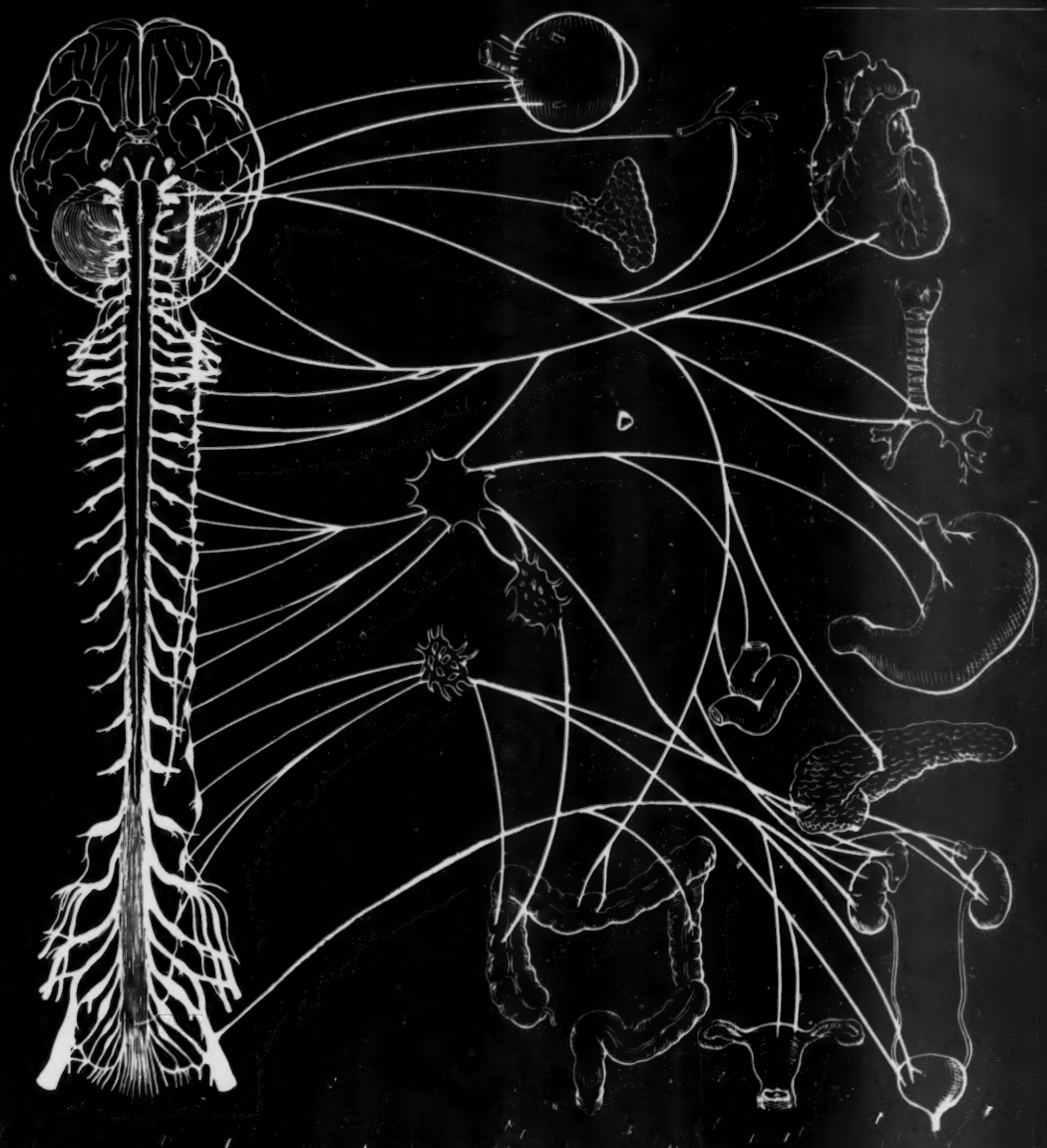
OCTOBER 4–9. American Academy of Pediatrics. Notice above.

OCTOBER 17–20. American Association of Blood Banks. Notice above.

OCTOBER 19–30. New York Academy of Medicine. Page xvii, issue of June 11.

OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

(*Notices concluded on page xiii*)



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NOTICES (*Concluded from page 1126*)

DISTRICT MEDICAL SOCIETY

MIDDLESEX SOUTH

SEPTEMBER 23.

NOVEMBER 18.

JANUARY 20. (Combined with the Auxiliary.)

MARCH 24.

MAY 12. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 2

THURSDAY, JULY 2

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, JULY 3

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

MONDAY, JULY 6

*8:30–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
12:00 m. Clinicopathological Conference (Boston Floating Hospital). Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, JULY 7

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Pediatric Rounds, Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical), Faulkner Hospital.

WEDNESDAY, JULY 8

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.
*4:00–5:30 p. m. Fracture Lecture. Boston City Hospital.

*Open to the medical profession.

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